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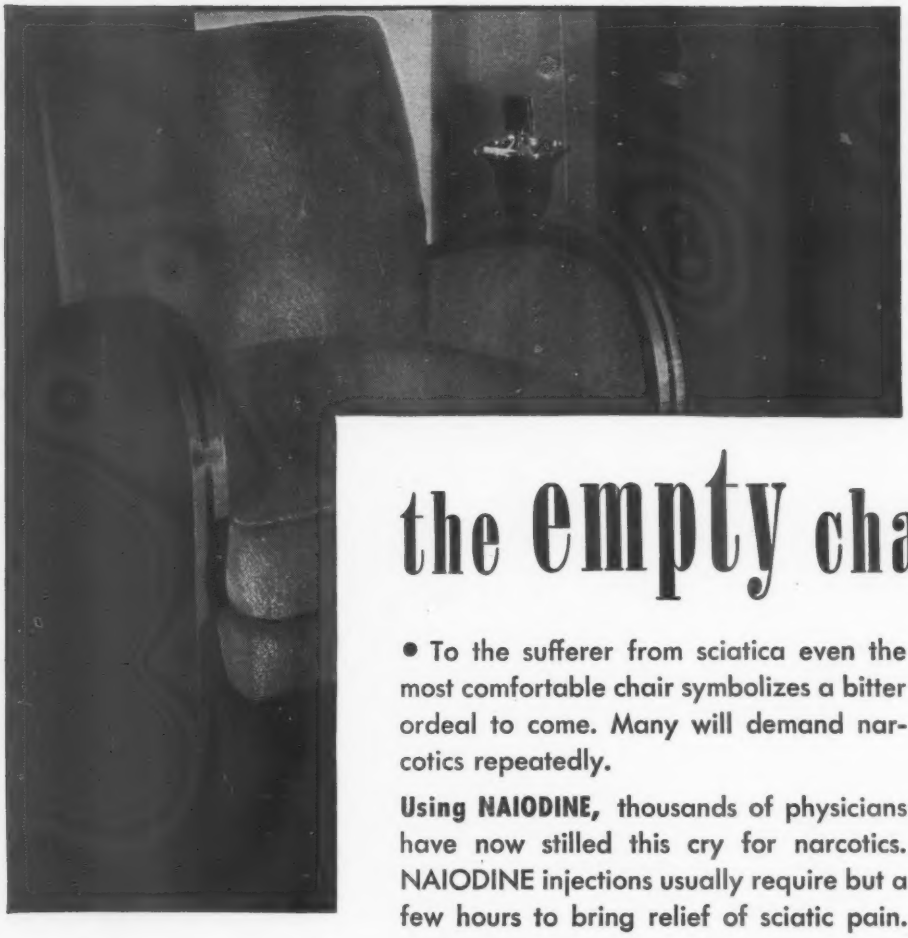

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1946

ORIGINAL ARTICLES

THE EFFECT OF DI-ISOPROPYL-FLUOROPHOSPHATE (DFP) UPON PATIENTS WITH MYASTHENIA GRAVIS*

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Di-isopropyl-fluorophosphate (DFP) is a compound (completely unrelated chemically to neostigmine or physostigmine) which has been shown to produce marked inhibition of serum, red cell, muscle and brain cholinesterase for long periods of time. The rates of restoration of these activities are very slow following administration of DFP and consequently the effects of DFP are far more prolonged than those of neostigmine or physostigmine.[9,16] When instilled into the conjunctival sac, 0.1% DFP produces intense miosis which may persist for days or weeks;[13] this action has been found to be of considerable value in the treatment of glaucoma and in overcoming atropine mydriasis.[13] When given systemically in small doses, its only detectable effects are the inhibition of plasma and then red cell cholinesterase; large doses produced stimulant effects upon skeletal muscle, and still larger doses lead to increased gastro-intestinal activity and (in some patients) effects upon the central nervous system. Because of its pronounced and prolonged anticholinesterase action, one of us (A. G.) considered it desirable to evaluate its effects upon patients with myasthenia gravis. Since many investigators believe that the symptoms of myasthenia gravis are due to an insufficiency of acetylcholine at the myoneural junction,† it seemed a matter of great theoretical importance to determine whether this new anticholinesterase agent was capable of increasing muscle strength in myasthenic patients. If DFP could be shown to possess this

* Supported in part by Kirby-McCarthy Funds.

† This insufficiency may be due to decreased formation of acetylcholine (faulty metabolism), to increased cholinesterase activity at the myoneural junctions or to decreased activity of acetylcholine due to the presence of antagonistic circulating curare-like substances.

property, its prolonged action would be important clinically by reducing the number of doses of drug needed and by providing a relatively constant effect throughout its period of action.

Method. In order to evaluate the efficacy of DFP, both subjective improvement noted by patients and observers and objective tests were employed.[19] Whenever possible, a comparison was made of the effects of DFP and neostigmine.

The effects of DFP or neostigmine upon muscle weakness, ptosis, swallowing function, appetite and hand dynamometer readings were noted by each patient and by one observer (J. T.) 3 times daily throughout the investigation. In addition, certain tests were performed in duplicate daily by each patient. These consisted of:

(*a*) *A Dynamic Finger Test.* The left arm was firmly enclosed in a plaster cast from above the elbow to the proximal phalanges to prevent movement of any muscles except those of the left forefinger. A light metal splint was then fastened with adhesive tape to the back of the forefinger to prevent flexion at any joint except at the phalangeal metacarpal. To the middle phalanx was attached a cloth ring, ½ inch wide; strong twine led from this to a pulley and a standard weight of 840 gm. The weight could thus be pulled up and down (on guide bars) by the finger and the rate and extent of this movement was recorded on kymograph paper by an ink writer attached to the weight. The maximal amplitude through which the finger could be flexed and extended passively was recorded before each test. A rate of 60 complete pulls per minute was then imposed upon the subject by a metronome. The subject was instructed to pull as vigorously as possible at this rate for 30 seconds.

(*b*) *A Static Finger Test.* The same apparatus (splints and weight) was used, but in this test the finger was pulled forward to an angle of 90° and the subject was instructed to hold the finger there with weight attached, as long as possible. Typical records of the dynamic and static tests are shown in Figure 1. In both the dynamic and static tests a rectangular area enclosing the maximal possible contraction for 10 seconds was measured by a planimeter for each test and this was considered as 100%; the area on the record enclosed in each 10 second portion of the 30 second test was measured similarly and the per cent of maximum is indicated as static or dynamic tests 1, 2 and 3 in Tables 2, 4 and 5. A normal individual can perform for many minutes without any decrease in performance, but myasthenic patients generally tire within 10 seconds.

(*c*) *Maximal Breathing Capacity.*[5] This was employed in some subjects as a dynamic vital capacity test[12] for measurement of strength of the respiratory muscles. The individual was instructed to breathe as rapidly and as deeply as possible for 30 seconds; the expired air was collected in a spirometer and the volume was measured for the first and second 15 second periods separately.

(*d*) *Hand dynamometer tests* were performed 3 times daily.

Patient L. G. had marked right monocular myasthenia gravis. In this case, in addition to the above tests, special ocular measurements were made so that objective comparison might be made of the effects of neostigmine and DFP on the extraocular muscles. Ocular muscle movements were measured by the screen and parallax method. The patient's head was placed in the head-rest of a Zeiss perimeter. The right eye was centered on the central fixation point when the right field of rotations was tested. The left eye was centered on testing the left field of rotations. The light of fixation was placed 30° from fixation in the 6 cardinal directions of gaze. By using the perimeter for measurements, some of the errors usually encountered in the estimation of squints and phorias were decidedly lessened. The distance from the eye to the point of fixation was constant in the 6 cardinal directions, and could be duplicated. The prisms were held approximately 2 cm.

from the eye and careful attention was paid to the position in which the prisms were held. Attempts were thus made to avoid the errors inherent in this method of measurement as described by Putnam and Quereau.[17]

In most of the subjects, mechanical myograms and electromyograms were recorded following supramaximal stimulation of the ulnar nerve; recordings were made from the fifth finger.[6] Rates of stimulation were 5, 20, 30, 40 and 55 per second.

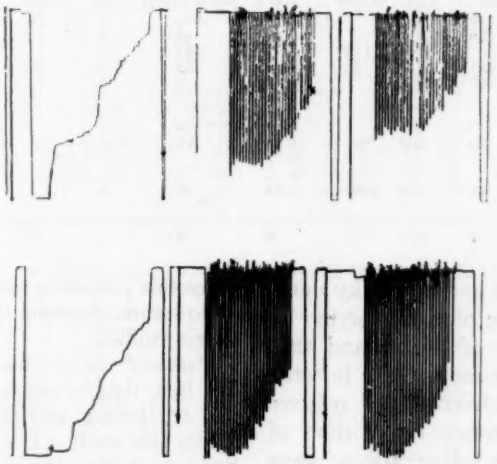

FIG. 1.—Static (left) and dynamic (center and right) work tests in Patient 6 before DFP (upper record) and 12 hours after the injection of 3 mg. of DFP (lower record).

The effect of DFP upon the function of the liver, kidneys, heart, hematopoietic systems and upon other body functions was evaluated carefully in each patient; these studies were essentially negative and have been reported elsewhere.[4]

Cholinesterase determinations were done before and during DFP therapy by a modification of Ammon's method.[16] It is of interest to note that plasma and red cell cholinesterase were within the normal range in all of our untreated myasthenic patients. In Table 1 are shown the physical characteristics of the 7 patients, the treatment course employed, and the lowest cholinesterase levels attained during DFP therapy. The interpretation of the measurement of cholinesterase activity, or indeed of enzyme activity in general, after therapy requires close scrutiny. When the substance which forms a readily reversible compound with cholinesterase and thus inhibits its activity, is administered therapeutically, the observed cholinesterase activity of the drawn serum or red cells depends upon the degree of dissociation of the cholinesterase inhibitor complex. This in turn depends, among other factors, on the dilution of serum or red cells in the final reaction mixture. Straus and Goldstein[20] have studied in detail the inhibition of dog and horse serum cholinesterase by physostigmine and have shown how the cholinesterase activity of the serum at any dilution may be corrected so as to represent the cholinesterase activity of the undiluted serum *in vivo*.

Neostigmine and other compounds have also been shown to form reversible complexes with cholinesterases.[2] However, no study of the effect of neostigmine on cholinesterase, similar to that of Straus and Goldstein on physostigmine, has yet been made. A number of determinations of cholinesterase activity in our patients showed, as might have been expected, that after the administration of neostigmine, the enzyme activity varied with

the dilution of the enzyme and the stage of the reaction. In view of these considerations and since we were not in a position to evaluate comprehensively the effect of neostigmine at various enzyme concentrations, we have not recorded any cholinesterase activities after neostigmine administration.

was possible in this patient. She required no further medication for 3 weeks, during which time her plasma cholinesterase activity rose from 2 to 122% and red cell cholinesterase from 37 to 50% of the control values. The myasthenic symptoms then reappeared. To evaluate possible psychic components in this patient's symptomatology she was given injections of sterile saline solution.

TABLE 1.—SUMMARY OF DFP THERAPY IN PATIENTS WITH MYASTHENIA GRAVIS

Patient	Sex	Age	Wt. lbs.	Total mg. DFP I.M.	Total mg. DFP Orally	DFP treatment period (days)	Period of observation post-treatment (days)	Lowest cholinesterase activity during DFP therapy: Plasma (%)	Lowest cholinesterase activity during DFP therapy: R.B.C. (%)	Remark
1. H. G.	F	25	148	11.0	..	29	295	2	24	Myasthenia gravis
2. S. C.	F	29	128	25.6	..	32	85	2	15	Myasthenia gravis
				17.0	168	117	67			
3. L. G.	M	54	131	3.0	28	8	38	0	26	Ocular myasthenia gravis
4. R. G.	F	21	107	2.5	..	1	5	5	74	Severe myasthenia gravis; patient requested release from hospital; died 6 months later
5. R. W.	F	25	90	5.0	92	26	11	0	25	Severe myasthenia gravis; died at home 1 month later
6. A. D.	F	38	93	13.0	60	50	30	0	5	Severe myasthenia gravis; died at home 1 month later
7. N. A.	F	35	94	5.5	12	6	3	1	18	Old myasthenia gravis

In contrast, Mazur and Bodansky showed that the inhibition of human serum by DFP is not readily reversible and that dilution of serum from a DFP injected animal does not influence the relative activity of cholinesterase on dilution of the serum.[16] These observations have been amply confirmed in the present study and accordingly cholinesterase determinations after DFP administration have been used as measures of the enzyme activity *in vivo* following DFP administration.

Results. *Patient 1* (H. G.) had myasthenia gravis of 4 years duration. Her outstanding symptoms were difficulty in swallowing and speaking, and weakness of arms, legs, neck and eyelids. Previous therapy had included irradiation over the region of the thymus gland and neostigmine. Electromyographic studies coupled with characteristic neostigmine, quinine and erythroidine tests confirmed the diagnosis of myasthenia gravis. This patient showed a dramatic improvement after the administration of 7 mg. of DFP intramuscularly over a period of 5 days, as judged by subjective symptoms, general appearance and hand dynamometer performances; no objective quantitative comparison with neostigmine

Since this procedure resulted in almost complete return of strength, the patient was no longer studied.

Patient 2 (S. C.) had developed ptosis of her lids, double vision, difficulty in speech and swallowing, and limb weakness 4 years before this study. For the past 3 years she had been taking 15 mg. of neostigmine bromide 6 to 8 times daily as her sole form of therapy; under this régime she had been able to continue in her secretarial position. The electromyograph, erythroidine and intocostrin (curare) tests, and the static and dynamic finger tests revealed a typical picture of myasthenia gravis. This patient was given a prolonged course of intramuscular and oral DFP therapy both as an in and out patient. As a rule, marked subjective and objective improvement followed its use. Of the hundreds of tests done upon this patient, several representative results are shown in Table 2. The static and dynamic finger tests indicated that the associated muscles improved upon DFP therapy almost to the same degree as during neostigmine treatment (Table 2). During DFP therapy, she was able to lead a normal life in the hospital without neostigmine for 2 weeks, though she had formerly required daily amounts of 120 mg. neostigmine bromide orally. However, when she returned to her position as

secretary and typist, she was unable to perform a full day's work without additional neostigmine. During a 3 week period, she received 1 or 2 injections a week of 2 to 3 mg. DFP intramuscularly. On the day of the injection she required little or no neostigmine, but within 1 to 2 days, 40 to 60 mg. daily were needed. Attempts to increase the dose of DFP intramuscularly led to severe nausea and vomiting. Later she was given daily oral doses of DFP, and this served to reduce the amount of neostigmine needed. This patient requested prolonged treatment with DFP because of visual blurring completely. Physical examination revealed ptosis of the right upper eyelid and weakness of the right inferior oblique and right inferior rectus muscles. The left eye was normal.

This patient had myasthenia gravis limited to the right eye since muscle function tests done upon the hands and fingers revealed no weakness even with prolonged testing. Consequently the comparison of the effectiveness of DFP and neostigmine was carried out entirely upon the extraocular muscles. Measurements were made before and 30, 35, 45 minutes and 6 hours after injection

TABLE 2.—EFFECT OF NEOSTIGMINE AND DFP UPON MUSCLE FUNCTION TESTS IN PATIENT 2 (S. C.)

				% of possible maximum by 10 second periods								
				Static test			Dynamic test			Dynamometer		
Date	Drug	Dose (mg.)	Hours after drug test was performed	1	2	3	1	2	3	R.	L.	R.B.C. Ch. E.
4/25/45	Neostigmine	1.5 (i.m.)	1½	97	97	91	98	96	88	55	64	*
4/27/45	DFP	3.0 (i.m.)	7	86	87	63	91	90	73	51	50	33%
5/3/45	DFP	3.0 (i.m.)	13	97	100	89	96	90	..	40	45	22%
				99	100	84	99	92				

* See under Methods for explanation of omission of cholinerase following neostigmine.

TABLE 3.—EFFECT OF NEOSTIGMINE AND DFP ON MYASTHENIC EXTRAOCULAR MUSCLES IN PATIENT 3 (L. G.)

	Without medication				After prostigmine (1.5 mg.)				After DFP (3 mg.)	
Direction of gaze	July 2	July 6	July 9	July 12	July 2 (30 min.)	July 9 (45 min.)	July 12 (35 min.)	July 12 (6 hrs.)	July 6 (45 min.)	July 7 (24 hrs.)
	Prism diopters									
Up and to right	3†	0	0	0	1†	0	3†	0	0	0
Horizontally and to right	1*	1*	1*	1*	0	1*	3*	1*	0	0
Down and to right	20*	15*	20*	15*	15*	15*	15*	20*	15*	15*
Up and to left	25†	25†	25†	25†	15†	15†	20†	25†	25†	25†
Horizontally and to left	8†	8†	12†	8†	5†	0	1†	3†	10†	10†
Down and to left	0	1†	0	2†	0	0	0	0	0	3*
Fissure size OD (mm.)	2	3	3	3	10	8	8	3	5	6
Fissure size OS (mm.)	10.5	10	11	9	10.5	9.5	9	10	9.5	9

* Right hyperphoria.
† Left hyperphoria.

the overnight effect of the drug; she felt much less weak upon awakening each morning than when maintained on neostigmine alone. In this patient, DFP definitely reduced the simultaneous neostigmine requirement, but could not replace it entirely because of the development of nausea and vomiting (not always controlled by atropine).

Patient 3 (L. G.) had complete ptosis of his right eyelid associated with marked visual blurring when this lid was propped open. Previous therapy had consisted of the administration of 15 mg. of neostigmine bromide 6 times daily which relieved this ptosis in large part but did not relieve his of 1.6 mg. neostigmine on each of 3 occasions. On different days, measurements were made before and after the intramuscular injection of 3 mg. of DFP. In addition the width of the palpebral fissures was measured before and after each injection. The results are recorded in Table 3.

It is evident that neostigmine had only a slight effect upon the myasthenic extraocular muscles, but a definite effect upon the levator palpebrarum. DFP had less effect than neostigmine on the extraocular muscles and the levator despite the fact that large enough amounts of DFP were given to cause repeated nausea and vomit-

ing. Though less powerful, the DFP action was more prolonged, and some effects persisted for 24 hours whereas that of neostigmine was gone within 6 hours. It is of interest to note that local administration of neostigmine (by iontophoresis of a 5% solution through the right lid) produced definite improvement locally for less than 6 hours.

Patient 3 (R. G.) had marked muscular weakness throughout her body for the past 2 years. She had great difficulty in speaking and swallowing and on several occasions had experienced attacks of dyspnea and tightness in the chest. Her therapy has consisted of 6 to 7 hypodermic injections of 0.5 mg. of neostigmine methyl sulfate and two 15 mg. oral tablets of neostigmine bromide daily. The electromyogram, static and dynamic finger tests, and maximal breathing capacity were all indicative of severe myasthenia gravis and all of these improved markedly following the injection of 1.5 mg. of neostigmine methyl sulfate.

After an injection of 2.5 mg. DFP (in water) intramuscularly, she became nauseated and vomited several times. She complained of dizziness, light headedness and faintness. Attempts to obtain objective measurements of strength of her finger or respiratory muscles failed because of weakness, malaise and inability to sit in a chair. Dynamometer readings were 0. She was given neostigmine every 2 hours again and after 36 hours had regained her previous state of strength.

In this patient, incapacitating side effects of DFP in small dosage prevented an adequate therapeutic trial with this agent. It was apparent, however, that it was unable to substitute for neostigmine even for 4 hours, and that its side effects lasted 24 to 36 hours. The patient refused further treatment; she died at home 6 months later.

Patient 5 (R. W.) had severe myasthenia of 7 years duration. In the past 2 months she had several periods of respiratory failure and asphyxia. She had been taking 15 mg. of neostigmine orally every 3 hours during the day and every 6 hours at night. Recently she failed to get relief from even 30 mg. of neostigmine orally and hypodermic injections have been required several times daily. The electromyogram, static and dynamic finger tests and hand dynamometer tests were all confirmatory of the diagnosis; these returned toward normal following an injection of neostigmine.

A comparison of the effects of neostigmine and DFP upon this patient are shown in Table 4. Myasthenic symptoms were so severe in this patient that control studies could not be performed with all drugs discontinued. However, upon 1 occasion, neostigmine was withdrawn for a period of 6 hours; this led to extreme weakness. As shown in Line 1 of Table 4 the static finger test at this time was only 9% of the maximal possible contraction, the dynamic test was 15% and the dynamometer reading was 0. The next 4 lines of Table 4 show the values recorded upon 4 different days 15 to 60 minutes after the injection of 1 and 1.75 mg. of neostigmine intramuscularly; marked improvement is evident. The last 3 lines present the values recorded following the administration of DFP; in each of these no neostigmine had been given for 3 to 4 hours. It can be seen that, while DFP produced considerable improvement in all the tests as compared with the control values, it never improved the patient's static, dynamic and dynamometer scores to the extent that neostigmine did. However, the

TABLE 4.—EFFECT OF NEOSTIGMINE AND DFP UPON MUSCLE FUNCTION TESTS IN PATIENT 5 (R. W.)

Date 1945	Drug	Dose (mg.)	Hours after drug tests were performed	% of possible maximum by 10 second periods: Static test 1	Static test 2	Static test 3	Dynamic test 1	Dynamic test 2	Dynamic test 3	Maximal breathing capacity 1	Maximal breathing capacity 2	Dynamometer R.	Dynamometer L.	R.B.C. cholinerase
6/27	Neostigm.	15 oral	6	9	9	5	15	12	8	5	13	0	0	
6/23	Neostigm.	1.0 i.m.	¼	93	86	62	79	71	56	92	87	45	40	
6/26	Neostigm.	1.5 i.m.	¼	90	90	90	99	100	72	..	..	45	35	
6/25	Neostigm.	1.0 i.m.	¼	95	95	97	97	80	..	77	95	45	32	
6/28	DFP	3.0 i.m.	23	9	19	..	14	20	..	80	59	10	0	60%
6/29	DFP	2.0 i.m.	1¼	62	59	53	47	48	..	106	84	20	10	40%
7/19	DFP	4 oral	2	45	43	43	57	56	..	81	67	20	0	25%

respiratory muscles were maintained in relatively good strength by DFP, despite a more marked decline in the second of the two 15 second periods.

This patient was highly coöperative and intelligent and it is felt that she performed to the best of her ability at all times. In this case, DFP was unable to substitute even in part for neostigmine (see discussion). This patient was returned to neostigmine therapy, but died in her sleep at home a few weeks later.

DFP given alone (even to the extent of lowering red cell cholinesterase to 5% and of producing nausea and vomiting) was never able to raise the scores to the high levels attained following the addition of neostigmine. This table indicates that combined therapy of DFP and neostigmine may yield more improvement than either drug alone. This patient died at home 1 month later while on neostigmine therapy.

One experiment upon this patient raises some pertinent questions regarding the

TABLE 5.—EFFECT OF NEOSTIGMINE AND DFP UPON MUSCLE FUNCTION TESTS IN PATIENT 6 (A. D.)

				% of possible maximum by 10 second periods										
				Static test			Dynamic test			Maximal breathing capacity		Dynamometer		
Date 1945	Drug	Dose (mg.)	Hours after drug tests were performed	1	2	3	1	2	3	1	2	R.	L.	R.B.C. cholinerase
4/23	Neostigm.	15 oral	4	87	70	56	82	70	55	..	..	45	35	
5/3	Neostigm.	1.5 i.m.	2	94	94	92	92	83	59	78	56			
5/3	Neostigm.	1.5 i.m.	2½	100	100	87	89	84	72	..	..	50	50	
5/9	Neostigm.	15 oral	1	96	85	87	91	73						
			1½	100	100	73	98	79	..	..	..	40	45	
5/10	Neostigm.	15 oral	2	93	99	100	96	100	65					
				98	100	91	100	99	..	..	..	40	45	
5/12	Neostigm.	15 oral	3	100	100	100	99	100	89					
				90	91	93	96	93	80	..	..	45	42	
4/24	DFP	3.0 i.m.	2½	87	66	..	72	60						
			4½	79	51	..	69	59	26	45	38	45	38	70%
4/29	DFP	2.0 i.m.	19	73	62	48	79	63	..	..	..	30	30	61%
			26	64	58	34	84	78	..	..	..	30	30	
5/6	DFP	3.0 i.m.	26	93	75	48	100	78	..					
			26½	93	67	..	87	82	..	..	..	30	32	25%

Patient 6 (A. D.) had double vision, difficulty in swallowing and talking, and generalized weakness. She had never had neostigmine therapy. Her myographic, electromyographic, static and dynamic finger, hand dynamometer and maximal breathing capacity tests were all indicative of myasthenia gravis. Intocostrin (curare) and erythroidine resulted in marked weakness in one-tenth the dose required to produce lid ptosis in normal individuals and her symptoms and tests improved greatly after an injection of 1.5 mg. neostigmine methyl sulfate.

In Table 5 are shown the scores attained after neostigmine on each of 6 days and those achieved after DFP had been administered alone on each of 3 days. With the exception of that given on April 23, 1945, all doses of neostigmine were administered after some DFP had been injected and the plasma and red cell cholinesterase were already at a low level. It can be seen that the administration of DFP was followed by scores as high as that produced by oral neostigmine on April 23. Figure 1 illustrates the improvement shown in her work tests after DFP. However, mechanisms of action of DFP and neostigmine in the treatment of myasthenia gravis. After treatment with DFP for a month, the plasma cholinesterase was 0 and the red cell cholinesterase was 14% of normal; nevertheless the patient was extremely weak (see Table 6 and Fig. 2). Neostigmine administered at this time improved her strength markedly. DFP administered 5½ hours later (after the neostigmine effect had apparently worn off) failed to produce further improvement. It has already been pointed out that DFP may be ineffectual if given after neostigmine[10] and this may account for its failure at this time. The reverse is not true, however, for neostigmine produced a considerable return of function at a time when the patient had been administered full doses of DFP, and the plasma and red cell cholinesterase were very low. This indicates either that blood cholinesterase levels are no index of muscle cholinesterase or that neostigmine acts by some mechanism other than by inactivating cholinesterase. This point is discussed later.

Patient 7 (N. A.) had developed weakness of her arms, legs and eyelids and difficulty in chewing and swallowing 14 years previously. Her disease has not progressed for 2 years. An injection of a small amount of erythroidine aggravated her weakness. Her electromyogram was atypical in that the first 3 action potentials of each series increased following supramaximal repetitive nerve stimulation (similar to the process of facilitation described by Harvey *et al.*[7] in his patient B. W.). The static and dynamic finger tests and the hand dynamometer test revealed marked muscle weakness. However only slight improvement followed the administration of neostigmine. This patient could not be classified at this time as a typical case of myasthenia gravis. She was given DFP only in the hope that some unexpected improvement might result. Subjective and objective studies showed no improvement or deterioration in her condition following DFP, except for occurrence of more side effects with the latter drug.

TABLE 6.—(COMPARISON OF EFFECT OF DI-ISOPROPYL FLUOROPHOSPHATE AND NEOSTIGMINE ON MUSCLE STRENGTH AND BLOOD CHOLINESTERASE)

Drug	Time	Cholinesterase (%)		% of possible maximum by 10 second periods						Maximum breathing capacity
				Static test			Dynamic test			
		Plasma	R.B.C.	1	2	3	1	2	3	
Previous DFP	9–10 A.M.	0	14	54	47	25	58	55	..	41
Neostigmine, 1 mg. i.m. . .	11:03 A.M. 11:45 to 11:50 A.M.	..	..	92	88	89	74	60	44	52
	1:04 P.M.	2	12							
	1:15 to 2:00 P.M.	..	..	86	87	86	60	46	..	51
	4:30 P.M.	..	..	65	43	..	42	34		
DFP, 4 mg. oral	4:35 P.M. 10:00 to 10:15 P.M.	..	..	48	39	13	38	23	..	41

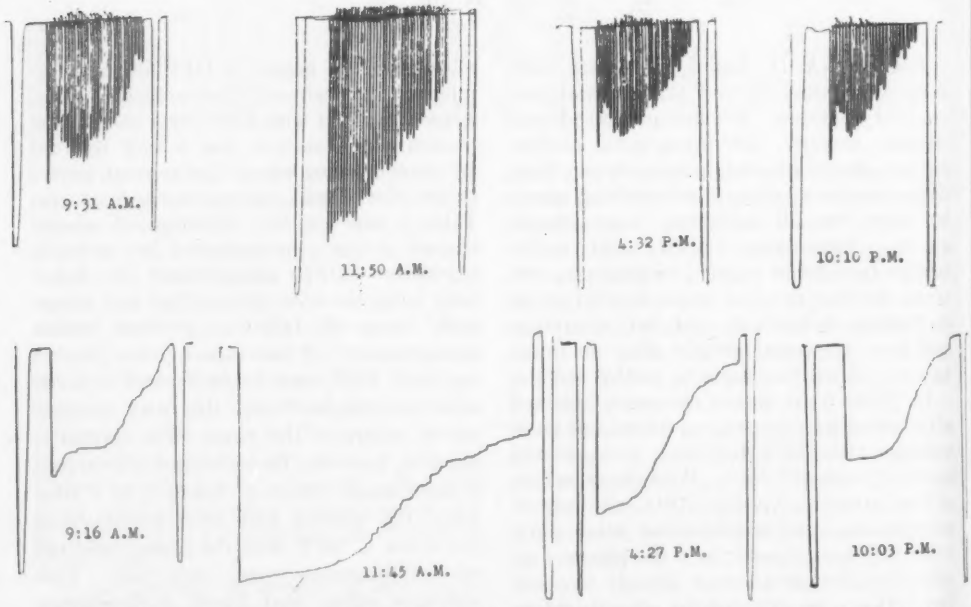

FIG. 2.—Dynamic (upper records) and static (lower records) work tests on Patient 6. The first pair (upper and lower) was recorded at 9:30 A.M. At 11 A.M., 1 mg. neostigmine was injected intramuscularly; the second pair of records was recorded 45 to 60 minutes later. The third pair was recorded at 4:30 P.M., when the neostigmine effect had largely worn off. Immediately thereafter 4 mg. DFP was given orally and the last pair was recorded at 10 P.M. For further discussion, see text.

Discussion. It has been shown by these studies that DFP, an anticholinesterase agent entirely unrelated chemically to neostigmine or physostigmine, is capable of increasing muscle strength in some myasthenic patients. Since the only detectable effects of DFP administered in low dosage appear to be due to its anticholinesterase activity,[4,16] this reëmphasizes that the fundamental defect in myasthenia gravis is intimately related to a deficiency of acetyl choline and that its symptomatic treatment is likewise related to the maintenance of adequate acetylcholine levels at the myoneural region. This "deficiency" of acetylcholine may be due to inadequate synthesis of acetylcholine or to the presence of an antagonistic curare-like substance; this investigation contributes nothing to strengthen or weaken either of these concepts.

However, it does raise the question as to the mechanism of action of neostigmine; for ample subjective and objective evidence has been presented here to show that DFP does not restore muscle power in myasthenic patients to the same degree as does neostigmine. These observations have been confirmed by Harvey and coworkers[8] who found that intraärterial injections of DFP into localized areas did not produce the *full* improvement in strength and in muscle action potentials that neostigmine did. The question arises as to why DFP, which is capable of lowering plasma and red cell cholinesterase activity to zero, affords less symptomatic relief to myasthenic patients than does neostigmine (the decreases in cholinesterase activity following neostigmine, though not determined precisely, were apparently not of this magnitude). Several explanations may be advanced for this unexpected finding. First, it is possible that the distribution of these compounds in the body is greatly influenced by their physicochemical properties. DFP is highly lipoid soluble whereas neostigmine has a high aqueous solubility. Thus, DFP may readily gain access to nervous tissue in experimental animals,[9,16] and normal subjects and myasthenic patients receiving DFP may show evidence of central nervous effects, an action not shared by neostigmine in ordinary doses.[4] It is possible that neostigmine may have a negligible distribution in the central nervous system whereas it might readily gain intimate contact with the myoneural junction. In support of the view that the relative therapeutic efficacies of DFP and neostigmine are the result of differences in drug distribution throughout the body are the observations of Harvey *et al.*[8] When large amounts of DFP were injected into the brachial artery of myasthenic patients, muscle strength and muscle action potentials were improved far more than by systemic administration of the drug. Thus it may be assumed that when a sufficient amount of DFP gains access to the myoneural junction, muscle strength is improved almost but not entirely to the same extent as by neostigmine. Unfortunately, doses of DFP large enough to produce such improvement throughout the body cannot be given systemically because of the untoward effects of DFP in large doses upon the gastro-intestinal tract and nervous system.

A second explanation might be offered for the finding that neostigmine is more potent than DFP in the relief of myasthenic symptoms. Neostigmine may have in addition to its anticholinesterase properties a direct action upon skeletal muscle that is not shared by DFP. Few unequivocal experiments have been performed to settle the question of whether direct muscular effects are produced by anticholinesterase agents. So far as their effects upon the circular muscle of the iris is concerned, it has been shown by Anderson for physostigmine[1] and more recently by Leopold and Comroe for neostigmine,[14] and for DFP[13] that these drugs become incapable of producing pupillary constriction when the iris is cut off from tonic parasympathetic impulses by ciliary ganglionectomy. So far as skeletal muscle is concerned, Langley and Kato[11] were unable to detect any contraction of de-

nervated gastrocnemius muscles following the application of physostigmine. However, Brown and Harvey[3] noted that physostigmine produced increased contraction of the denervated *extraocular* muscles, though this effect was not noted when other skeletal muscles were employed. More recently Riker and co-workers[18] stated that they have demonstrated a direct action of neostigmine upon striated muscle fibers. Clearly further quantitative comparisons are needed of the direct effects of physostigmine, neostigmine and DFP upon skeletal muscle.

The fallacy of relating the effects of an anticholinesterase agent upon plasma cholinesterase to its pharmacodynamic actions has already been pointed out.[9,16] The above studies show that it is equally fallacious to judge therapeutic efficacy by this criterion. Human plasma cholinesterase is more highly susceptible to inactivation by DFP than is human brain or muscle cholinesterase.[9,16] Thus, even neglecting the added complications of bodily distribution, plasma cholinesterase would be largely inhibited before tissue cholinesterases are significantly affected. Moreover, cholinesterases in different tissues vary so greatly in their rates of regeneration following inactivation by DFP[9,16] that the enzymatic activity in one tissue cannot possibly be estimated from the analysis of another even though their susceptibilities to inactivation are similar. Thus, the measurement of the cholinesterase activity of erythrocytes affords no knowledge of the status of muscle or brain cholinesterase when DFP is given over a period of days even though the sensitivities of the enzymes at these varied sites fall in the same range.

It has been shown that the DFP-cholinesterase complex is not readily reversible and dilution has no effect upon this reaction. We have already pointed out the uncertainties in using the determinations of cholinesterase activity after neostigmine therapy; the *in vitro* analysis of cholinesterase values in blood taken following neostigmine administration may yield figures that are considerably above or below the actual enzyme activity in the body, depending upon numerous factors such as dilution, pH and time.

The evaluation of DFP as a therapeutic agent in severe myasthenics is complicated by the fact that neostigmine protects cholinesterase from inactivation by DFP. Koster[10] first demonstrated that animals which had received physostigmine were more resistant to the lethal actions of DFP. Leopold and Comroe[15] have shown that previous ocular administration of physostigmine prevented the characteristic prolonged intense miotic action of DFP, administered at the time of maximal neostigmine miosis. Our Patient 5 (R. W.) could not be deprived of neostigmine for more than a few hours and it is possible that the presence of this reversible inhibitor blocked the effects of subsequently administered DFP. This fact may have some bearing on the failure of DFP in patients with myasthenic symptoms so severe that neostigmine can never be discontinued. Harvey and co-workers have confirmed this by demonstrating that the intraarterial injection of DFP failed to produce its characteristic prolonged effect in patients who had received neostigmine a short time previously.[8]

From the practical point of view, DFP possesses one main advantage, namely its prolonged action. This may enable a patient to avoid marked fluctuations in strength during the daytime and to awaken in the morning with considerably less fatigue than if the short-acting neostigmine alone is used. In our experience, simultaneous use of DFP and neostigmine often resulted in a definite reduction of neostigmine dosage and this combination may prove to be useful in the treatment of myasthenia gravis. However, in view of the marked gastro-intestinal disturbances produced by DFP it is obvious that a compound with a more specific action on the myoneural junction is desirable. Such an agent may be found among the many possible congeners of DFP which are under investigation.

It has been our experience from this study that an evaluation of the effectiveness of drugs in this disease can only be made after considerable experience in the design and interpretation of objective tests has been acquired. Spontaneous remissions in myasthenia are too frequent and unpredictable to permit assay by the patient's subjective impressions alone. Patients with myasthenia gravis want desperately to get well and the psychic effect of any new measure (medical or surgical) may be tremendous.

Conclusions. 1. Di - isopropyl - fluorophosphate (DFP), though entirely unrelated chemically to neostigmine, is capable of lowering plasma and red blood cell cholinesterase activity in man to a marked extent and for prolonged periods, and of improving muscle strength in patients with myasthenia gravis.

2. DFP was used in the treatment of 7 patients with myasthenia gravis. Two patients received little or no benefit from DFP, 2 received considerable improvement, 1 received marked beneficial effects and in the other 2 the effects were obscured by peculiarities in the natural cycle of the disease. In no case did the objective or subjective improvement following DFP equal or exceed that produced by neostigmine. Attempts to give larger doses of DFP resulted in marked nausea and vomiting, and symptoms referable to the central nervous system.

3. Despite the fact that DFP lowered plasma cholinesterase to zero, it produced less improvement than did neostigmine. The potentialities of a drug for treating myasthenia gravis clearly cannot be gauged by its effect upon plasma cholinesterase.

4. The possible reasons for the superiority of neostigmine over DFP in the treatment of myasthenia gravis are discussed.

5. As a practical treatment, DFP may be utilized in non-toxic doses to obtain its prolonged effect, at the same time that neostigmine is used to obtain its characteristically stronger action.

REFERENCES

1. Anderson, H. K.: J. Physiol., **33**, 156, 414, 1905.
2. Bodansky, O.: Science, **102**, 517, 1945.
3. Brown, G., and Harvey, A. M.: J. Physiol., **99**, 393, 1941.
4. Comroe, J. E., Jr., Todd, G., and Koelle, G.: J. Pharmacol. Exp. Ther., in press., **87**, 281, 1946.
5. Cournand, A., and Richards, D. W., Jr.: Am. Rev. Tuberc., **44**, 26, 1941.
6. Harvey, A. M., and Masland, R. L.: Bull. Johns Hopkins Hosp., **68**, 81, 1941.
7. Harvey, A. M., Lilienthal, J. L., and Talbot, S. A.: Bull. Johns Hopkins Hosp., **69**, 547, 1941.
8. Harvey, A. M., Jones, B. F., Talbot, S., and Grob, D.: Proc. Fed. Am. Soc. Exp. Biol., **5**, 182, 1946.
9. Koelle, G., and Gilman, A.: Personal communication.
10. Koster, R.: Proc. Fed. Am. Soc. Exp. Biol., **5**, 186, 1946.
11. Langley, J. N., and Kato, T.: J. Physiol., **49**, 410, 1914–15.
12. Laszlo, D., and Redlich, F. C.: Am. J. Med. Sci., **203**, 693, 1942.
13. Leopold, I. H., and Comroe, J. H., Jr.: Arch. Ophth., **36**, 1, 17, 1946.
14. Leopold, I. H., and Comroe, J. H.: Proc. Soc. Exp. Biol. and Med., **60**, 382, 1945.
15. Leopold, I. H., and Comroe, J. H., Jr.: Unpublished observations.
16. Mazur, A., and Bodansky, O.: J. Biol. Chem., **163**, 261, 1946.
17. Putnam, O. A., and Quereau, J. V.: Arch. Ophth., **34**, 7, 1945.
18. Riker, W. F., Wescoe, W. C., Cattell, McK., and Schorr, E.: Proc. Fed. Am. Soc. Exp. Biol., **5**, 199, 1946.
19. Schlezinger, N. S.: Arch. Int. Med., **65**, 60, 1940.
20. Straus, O. H., and Goldstein, A.: J. Gen. Physiol., **26**, 559, 1943.

CLINICAL AND ROENTGENOLOGIC ASPECTS OF COCCIDIOIDOMYCOSIS

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Coccidioidomycosis is an infection caused by the fungus *Coccidioides immitis*. It was first reported in Argentina in 1892 by Posadas[14] and Wernicke,[21] and in this country by Rixford[15] in 1894. Until 1936, the rather common and frequently fatal coccidioidal granuloma was the only phase of coccidioidal infection recognized clinically. At that time, and in subsequent publications, Gifford and Dickson[8,9,11] identified "valley fever" or "desert fever" as the initial or primary infection with *Coccidioides immitis*. This had been a common but poorly understood endemic disease long familiar to residents of the San Joaquin Valley in California. Its relationship to coccidioidal granuloma was thus established and provided the basis for present knowledge of the pathogenesis and natural history of coccidioidomycosis.

So far as is definitely known, coccidioidomycosis in this country occurs in several rather sharply limited areas. These are characterized climatologically by long, hot, dry, dusty summers, and a low annual rainfall. They include the southern and western parts of the San Joaquin Valley in California, parts of southern Arizona and western Texas. Adjacent regions in Utah and New Mexico with similar climatic and geographic features have been regarded as probable endemic areas, but evidence establishing them as such is thus far inconclusive, and they have not been important sources of coccidioidal infection.

Until recently, coccidioidomycosis attracted little interest among physicians in this country for several reasons: (1) The source of the infection is confined to a few sharply limited geographical regions. (2) Even in such regions, due to the mildness of the primary respiratory infection, many infected persons do not seek medical attention. Only the more severe or prolonged infections are likely to be seen by physicians, and in only a small percentage of these are the necessary facilities available for establishing the diagnosis. (3) Much that is new concerning coccidioidal infection from a clinical and roentgenologic standpoint dates from the fairly recent publications of Dickson and Gifford and has not yet diffused much beyond investigators and interested physicians, who encounter the disease in endemic areas.

As a result of war-time conditions, coccidioidomycosis has assumed considerable importance, and its endemicity is no longer an excuse for indifference regarding it. The Southwest has been an important army training area, and many installations have been established in localities where the disease is endemic. This situation has provided for a sustained increase in the incidence of the disease, due to the continuous influx of non-immune new arrivals into such areas. The likelihood of exposure is considerable and is increased with the duration of residence. The disease may be acquired in an endemic locality but manifested in a distant non-endemic region where it is unknown or unrecognized. Such a possibility confronts those in the military service, their families which in many instances accompany them, and innumerable civilians who have migrated to endemic regions where they are transiently employed in

various war-time projects. Not a few such areas have been and will continue to be attractive winter and health resorts with a large transient population of tourists and health seekers from various parts of the country. Thus, acute or chronic coccidioidomycosis may be encountered in individuals far removed from endemic areas. Moreover, inactive pulmonary residues, such as coccidioidal cavitation nodular pulmonary lesions may persist for months or years in apparently healthy persons who may or may not give a history of primary infection. The recognition and interpretation of such lesions is of the utmost importance if serious errors in diagnosis, treatment and prognosis are to be avoided. Without a doubt such lesions have been and will continue to be a basis for unwarranted compensation claims against the Government and might conceivably provide some problems in the realm of industrial compensation insurance. Knowledge of their significance and potentialities acquired by prolonged observation of such lesions is the only basis for an intelligent and equitable settlement of such claims. Army Medical Officers, Veterans Administration doctors and civilian physicians should be sufficiently familiar with the disease to recognize it in its various phases and especially its residual pulmonary lesions.

The purpose of this paper is to emphasize: (1) The increasing general importance of the disease and the necessity for its recognition wherever it may be encountered. (2) To review in the light of our own experience the salient clinical, laboratory and roentgenologic features of the disease. (3) To summarize the essential requirements of diagnosis and to indicate the relative value and limitation of various diagnostic procedures.

The present series consists of 77 cases admitted to an Army Air Force Regional Hospital in southern Arizona between August 1942 and August 1944, in which the diagnosis of coccidioidomycosis was confirmed either by coccidioidin serologic tests or cultural studies. This number affords no basis for an accurate estimate of the incidence of coccidioidal infection at this installation. It obviously does not include asymptomatic infections or a considerable number of probable coccidioidal infections in which, however, the diagnosis was questionable. All cases were sporadic and were distributed throughout every month in the year. In the months from July through December, 57 cases (74.1%) occurred, the peak of incidence being in August (13%) and September (14.3%); 68.8% of the patients were white, and 31.2% were colored. The incidence among the Negro troops was 3 times that among the white in proportion to their relative number at this installation. The period of hospitalization averaged 42 days. 72 patients with acute, uncomplicated coccidioidomycosis recovered completely. Of 5 patients with dissemination, 2 recovered completely, and 1 with dissemination to the meninges has apparently recovered. Two patients with dissemination died. Ten (13%) had some type of residual pulmonary lesion revealed by Roentgen ray. Of these, 4 (5.2%) had pulmonary nodules, and 6 (7.8%) showed pulmonary cavitation. In addition to the 77 hospitalized patients studied, clinical and roentgenographic material was available on approximately 200 patients, chiefly out-patients with residual pulmonary lesions, observed in southern Arizona during the period from 1941 to 1945. These include military personnel, civilian dependents and civilian employees. When suitable, roentgenographic material from this group has been used to illustrate some of the late lesions of coccidioidomycosis.

Clinical Types of Coccidioidomycosis. Several clinical types of coccidioidomycosis are recognized: A. The initial or primary infection is always respiratory and incurred by inhalation of chlamydospores in contaminated dust. It is focalized in the lungs, and in most instances subsides spontaneously and without sequelæ. It may be entirely asymptomatic. This is

the usual type of infection among residents of endemic areas. Subclinical and unrecognized, its occurrence in an individual may be indicated only by demonstrable sensitivity to coccidioidin and uncommonly by residual pulmonary lesions revealed by Roentgen ray examination. Approximately 10 to 15% of individuals with 1 year's residenee in an endemic area will acquire such infection, and after 10 years' residence approximately 80 to 90% will have acquired the infection.[1,19] Of 200 enlisted men in the Medical Detachment of the hospital with up to 18 months' residence in the area and without a history of clinical infection, 12.5% reacted positively to the cutaneous coccidioidin test.

B. The type most frequently encountered clinically is an acute self-limited respiratory infection manifested predominantly as a bronchitis, pleuritis or pneumonitis. It is often clinically indistinguishable from more prevalent non-specific respiratory infections or primary atypical pneumonia, and diagnostic confirmation is not obtained ordinarily in civilian practice.

C. When the initial respiratory infection is associated with allergic phenomena such as erythema nodosum or erythema multiforme it may be easily recognized clinically and has been referred to variously as "San Joaquin Valley fever," "desert fever," "valley fever," and "desert rheumatism." Approximately 18% of the cases in our series were of this type—6.5% with erythema nodosum and 12% with other types of erythematous skin lesions. This incidence is slightly higher than that reported by Smith[18] and is nearer the figures reported by Goldstein and Louie,[12] who found erythema nodosum in 19% of their patients and in approximately 25% of all cases there were cutaneous manifestations.

D. While complete recovery is the rule, in an unknown proportion of cases (13% in our series) the primary infection results in apparently benign, persistent residual pulmonary lesions, notably cavitation or nodules usually unaccompanied by constitutional symptoms or signs and revealed by Roentgen ray examination of the chest.

E. In rare instances the initial infection does not subside but becomes progressive with widespread lymphatic and hematogenous dissemination. Any or all the organs of the body, with the notable exception of the digestive tract, may be Involved. The lungs, tracheobronchial, supraclavicular and cervical lymph glands, the meninges, skin and bone are especially vulnerable. The clinical features and course may vary considerably, depending upon the extent of dissemination or the dominant localization. In the cases observed by us, the striking clinical manifestations were those of generalized miliary dissemination in 2, persistent massive pleural effusion in 1, pulmonary and glandular localization in 1, and meningeal in 1. Meningeal localization may be the only demonstrable site of spread or it may be simply a part of a generalized dissemination. The disseminated form usually runs a protracted course and terminates fatally in about one-half the cases. Miliary tubercles, confluent areas of caseation nenecrosis and typically granulomatous lesions occur in the involved organs. The disease may simulate and at times be indistinguishable, clinically and pathologically, from tuberculosis, differentiation, depending upon recovery of the etiologic agent.

It should be borne in mind that the disseminated phase, in the great majority of cases, develops sometime during the acute, primary infection and represents a continuous progression of the disease. Dissemination, if it is going to occur, usually takes place within the first few weeks or months, and thereafter its likelihood diminishes. It should be suspected in the presence of prolonged high fever or symptoms and signs indicative of meningeal, skeletal or cutaneous involvement. The coccidioidin serologic test is of help and may be decisive in detecting dissemination not clinically evident. Dissemination, after several years, as a result of endogenous reactivation, while admittedly a possibility, must

be extremely rare if it occurs at all. Present available evidence upon this point is meager and unconvincing.

Clinical Features. A. *Pain.* The most frequent, and in many cases, the predominant symptom in the acute infection is thoracic pain. It occurs in from 75 to 85% of patients. In most instances (54.5% in our series) pain is severe and pleuritis in character. In 2 instances patients were referred to the hospital from the dispensary with a diagnosis of fractured rib, although no history of injury had been elicited. When localized to the anterior chest, the pain may simulate anginal pain or the pain of acute pericarditis. In approximately 20% of our patients the pain was substernal or constricting in character or described chiefly as a dull, heavy sense of discomfort. While the acute pain usually subsides after several days, it is not uncommon to note residual vague chest pains or aching, persistent or recurrent for periods of several weeks to several months.

Some patients with subpleural nodular lesions complained of a dull, boring ache, usually referred to the shoulder or interscapular region, in most instances unassociated with evidence of clinical activity. Such pain may persist with varying intensity for several months at a time with ultimately spontaneous subsidence.

B. *Fever.* Fever was present in the majority of patients sometime during the course of their illness. In the ordinary uncomplicated cases the average duration was approximately 1 week. However, the fever was occasionally prolonged, and in disseminated cases persisted for months. There was nothing characteristic about the fever curve. A fact to remember in this connection is that a considerable number of patients (39% in our series) may be afebrile throughout the entire period of observation despite other symptoms and signs such as increased sedimentation rate and roentgenologic findings to indicate activity of the disease.

C. *Cough.* Less than half of our patients had any significant cough, and of these in only a small percentage was it productive. Sputum was usually scant, and even when obtainable examination for *Coccidioides immitis* was frequently unsatisfactory. Examination of fresh preparations is not reliable especially in inexperienced hands. Sputum examination is limited in usefulness by the infrequency with which satisfactory specimens are available in acute primary coccidioidomycosis and by the tedious cultural methods required to identify the organism. Failure to recover *Coccidioides immitis* from the sputum in cases with cavitation warrants an attempt to recover the fungus from gastric washing.

D. *Cutaneous Lesions.* The cutaneous manifestations associated with coccidioidal infection differ in character with the stage of the disease. In about 18% of our cases with acute primary coccidioidomycosis, cutaneous eruptions occurred. These included the typical erythema nodosum of "desert fever;" located symmetrically over the pretibial region, and to a less extent the thighs, and referred to colloquially in the San Joaquin Valley as "the bumps." This type of eruption occurred in 5 (6.5%) of the patients. In a larger proportion of cases, 9 (11.7%), a less well-defined erythematous eruption occurred. Few of these were fairly typical erythema multiforme, but others were generalized, irregular, papular erythematous lesions involving the entire trunk and sometimes were distinctly morbilliform in appearance. The erythematous skin lesions usually occurred within the 1st week of the initial infection and subsided within approximately 1 to 2 weeks. Such lesions are associated with hypersensitivity to coccidioidin, development of a high degree of immunity and resistance to dissemination. In disseminated cases granulomatous skin lesions, verrucous or papillary in character, single or multiple cutaneous cold abscesses and indolent sinuses may occur. Two of our disseminated cases had such lesions. From them *Coccidioides immitis* may be recovered. They are invariably metastatic and indicate dissemination.

F. *Arthritis.* Arthritis has been reported as occurring in approximately one-third of the cases and accounts for the term "desert rheumatism." The involved joints have been described as tender, painful on motion, and at times slightly swollen. Effusion ordinarily does not occur. Goldstein and Louie[12] reported some dull articular ache or pain during the course of the illness in 30% of their patients. These observers noted no swelling or tenderness, and the roentgenograms were uniformly negative. Joint symptoms usually subside within a month and without residual damage or deformity. We have been singularly unimpressed with arthralgia as a significant complaint in any of our patients, and in none were objective joint changes encountered. In fact, arthralgia, beyond what might occur in a variety of acute infections, was not observed. Rosenberg, Dockerty and Meyerding[17] state that joint symptoms are usually associated with erythema nodosum. However, Smith[19] states that arthritis may occur without skin manifestations while the latter without arthritis are very frequent. Bone and joint lesions characterized by redness, swelling, fluctuation, adjacent skin lesions with ulceration or sinus formation are not infrequent in the disseminated form of coccidioidomycosis. However, we encountered none in our series.

While general symptoms of infection, such as headache, malaise, myalgia, lassitude and weakness occur, they are neither as frequent nor conspicuous as in most respiratory infections of comparable severity. This observation has been commented upon by others.[5] The patients in general look and feel better than their clinical and roentgenologic findings would indicate. This is generally true, not only of the acute primary infections, but also of the disseminated form in which the disparity between the subjective complaints and objective findings has at times been striking. Hemoptysis is uncommon in the acute type of infection although it occurs at times with residual cavitation.

G. *Physical Findings.* Physical findings in acute coccidioidomycosis in the absence of the cutaneous manifestations are of little or no help from a diagnostic standpoint. Despite pulmonary involvement, dyspnea, cyanosis, tachycardia and evidence of systemic toxicity are either absent or minimal. In contrast to the frequency of pleuritic pain, a pleural friction rub is seldom heard. Rarely, massive pleural effusion occurs, but in most instances the amount of fluid is insufficient to detect on physical examination. Signs of cavitation in the late cases are usually absent despite the size of some of the cavities. Hilar lymphadenopathy is a fairly common roentgenographic finding, but peripheral lymph gland involvement is not encountered in the acute cases. However, in disseminated cases, unusually extensive lymphadenopathy may occur. In such cases it is usually most marked in the hilar, supraclavicular and cervical groups and may progress to abscess formation with draining sinuses.

H. *Laboratory Findings.* Except for the cultural and inoculation tests to which we will refer later, laboratory studies have little in the way of specific value in the diagnosis of coccidioidomycosis. There are, however, a few findings that are helpful diagnostically or as an index of activity of the disease. The leukocyte count is usually moderately elevated. Eosinophilia has been noted and occurred in 18 (23.3%) of our patients. All of these had eosinophil counts higher than 10%, the highest eosinophilia being 29%. Moderate to marked erythrocyte sedimentation rates were found in 75 of our patients (97.5%). This proved to be the most useful single index of activity and persisted in most instances long after complete subsidence of all the clinical findings with the exception of residual Roentgen ray findings.

There is some evidence to indicate that coccidioidomycosis occasionally may give rise to transient, false positive blood serologic tests for syphilis. Four patients in

our series had positive Kahn and Kline tests early in the course of their coccidioidal infection. In none was the Wassermann test positive. In 3 cases the duration of the positive serologic reaction persisted from 2 weeks to 1 month following which the tests became negative spontaneously. None of the patients had a history of syphilis, and clinical evidence was lacking in all cases. None of the more usual causes of false biologic positive tests could be demonstrated. In 1 case lues could not be excluded, although it was improbable. This patient (Case 3) had disseminated coccidioidomycosis, was critically ill, and although the Wassermann was negative, both the Kahn and Kline tests were 4+ on 3 different tests reported from different laboratories. Unfortunately verification tests were not obtained. Because of the possibility of syphilis complicating the coccidioidal infection, it was decided not to withhold antisyphilitic treatment. In view of subsequent experience, however, we feel that a longer period of observation would have revealed the true significance of the positive serologic tests in this case. The conclusion is obvious that great caution must be exercised in the interpretation of positive serologic tests for syphilis among patients with coccidioidomycosis. Reasonably prolonged observation and verification tests are indispensable in the solution of this problem.

Roentgenologic Features. GENERAL. Many physicians think of coccidioidomycosis as a disease which mimics tuberculosis. This generalization must be qualified by recognition of the of the fact that it is a disease which may simulate various types of acute pneumonic lesions in its earlier phases, and later may present film evidence which is similar to that in various forms of lymphoma, metastatic malignant lesions and primary malignant lesions. Bone lesions are absent in the primary phase of coccidioidomycosis, but in the disseminated type skeletal lesions may resemble various neoplastic lesions of the skeleton, non-tuberculous osteomyelitis and periostitis and other destructive lesions of bone and cartilage in addition to tuberculosis.

Roentgenologic findings of this disease have been presented[2–7,13,22,23] in medical literature of recent years. Comprehensive reviews of the literature are available in recent publications.[5,7] It is desired to stress in this discussion certain salient features of roentgenographic nature and to summarize information obtained by the study of patients with acute and late coccidioidal pulmonary lesions. A tendency for primary pulmonary coccidioidomycosis to follow one of five general patterns has been observed on the basis of serial film studies extending over months or years. A finding of interest is the seasonal incidence of new cases as reflected by records of the Roentgenologic Service. For example, recently in 12 consecutive months, during the period from May to October inclusive, 75 new cases were observed, while during the months from November to April inclusive only 38 new cases were encountered. The short incubation period (8 to 15 days) accounts for the close correlation of Roentgen ray and clinical signs to the months during which hot dry weather is prevalent.

Roentgenologic Findings in Primary Coccidioidomycosis. In the primary phase of this disease it is well agreed that Roentgen ray findings are limited to the thorax. Patients may complain of arthralgia in the initial days or weeks of their illness, but film evidence of organic change in skeletal structures at this time is lacking. Roentgenologic findings are variable as summarized in the 77 hospitalized cases indicated in Table 1. Attention is called to a small group of patients (2.6%) who were hospitalized for coccidioidomycosis but in whom no Roentgen ray signs of the disease could be recognized despite knowledge of characteristic clinical findings such as erythema nodosum and evidence of activity of the disease by skin testing and by serologic studies. On the other hand, knowledge gleaned from single films or the aggregate of findings on serial

films sometimes identifies involvement as coccidioidomycosis before other positive evidence appears. From the Roentgen ray viewpoint an element of confusion arises from the fact that a patient may first be examined in almost any phase of the disease. If such a patient is filmed at the onset, the pulmonary findings may be exactly the same as would be expected from the acute bacterial and virus pneumonias. This group of early cases has presented a recurrent problem, which has been solved only by serial films and by the combination of roentgenographic and clinical findings to achieve accurate differentiation. One can safely state that early primary pulmonary coccidioidomycosis and primary atypical pneumonia are 2 conditions which may produce a variety of similar appearances in the lungs and pleuræ.

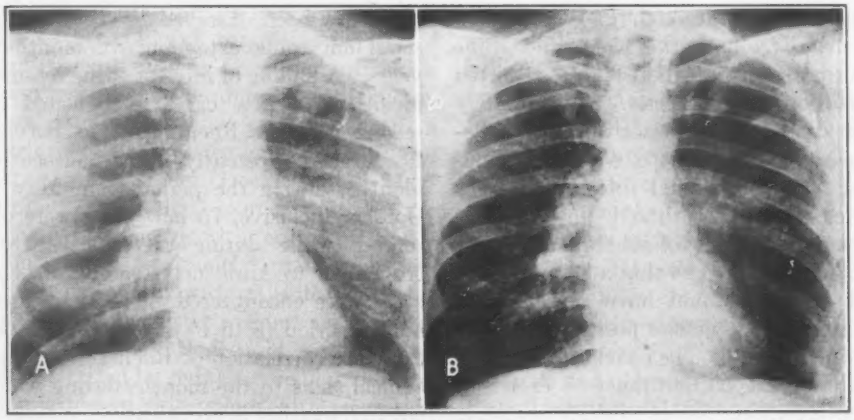

FIG. 1.—*A*, Acute bilateral pneumonitis. Minimal effusion, left. Hilar prominence bilaterally, predominantly left. *B*, After 15 days. Note tendency for nodular configuration opposite anterior end of 5th right rib. Persistent bilateral hilar accentuation. Increase in fluid accumulation in left pleural cavity. Findings disappeared after additional 3 months.

TABLE 1.—TYPES OF LESIONS IN PRIMARY COCCIDIOIDOMYCOSIS

	Per cent.
Pneumonitis	70.0
Adenitis	23.3
Cavitation	7.8
Nodules	5.2
Pleural effusion	2.6
Negative chest film	2.6

If a patient is seen somewhat later in the primary phase of pulmonary coccidioidomycosis the differential diagnosis on the basis of a single film may be impossible because of the similarity of the lesions to lymphoma, secondary malignant foci, or tuberculosis.

A. *Pneumonitis.* Acute pneumonitis in coccidioidomycosis may be nothing more than minimal increase in soft tissue prominence in one hilar area, or barely perceptible obscuration of hilar detail on one or both sides. This is a group of lesions which is easily missed on the basis of film evidence alone because of wide variations in prominence of hilar areas among normal persons. Aid is gained by comparison with the opposite hilus if the lesion appears to be unilateral, or by serial films, or both. More easily detectable pneumonic infiltration may be found in the perihilar area, or it may be subpleural. A dependable point regarding distribution of pneumonic foci is the fact that consolidation of an entire lobe is extremely rare. Multiple areas of infiltration may be visible in 1 lobe or in all lobes bilaterally at the time of onset of the disease (Figs. 1, 2, 3). Early pneumonic infiltration of lungs or hilar areas may resolve completely within 1 to 4 weeks. Commonly, complete resolution does not occur even though partial resolution is the rule

during the early weeks of the initial involvement. Once partial resolution has appeared the future pattern of involvement will depend on whether healing and fibrosis remain predominant or whether about the time the initial acute pulmonary infiltration begins to recede (Figs. 1 and 2). A significant fact in connection with adenitis is that prominent nodes may appear in both the hilar and mediastinal

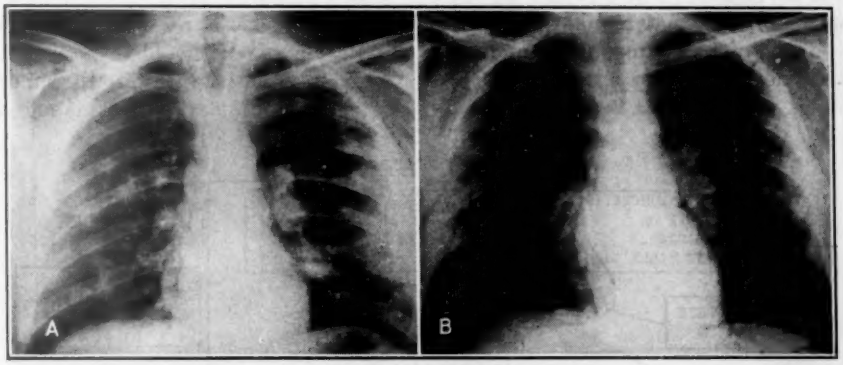

FIG. 2.—*A*, Admission film revealed scattered focal acute pneumonic infiltration in all lobes bilaterally, with slight bilateral hilar prominence. *B*, After 17 days. Pneumonic foci had partially resolved, with more nodular appearance. Hilar involvement, particularly on left, showed marked increase. Ten weeks later this patient showed no significant residue in the thorax.

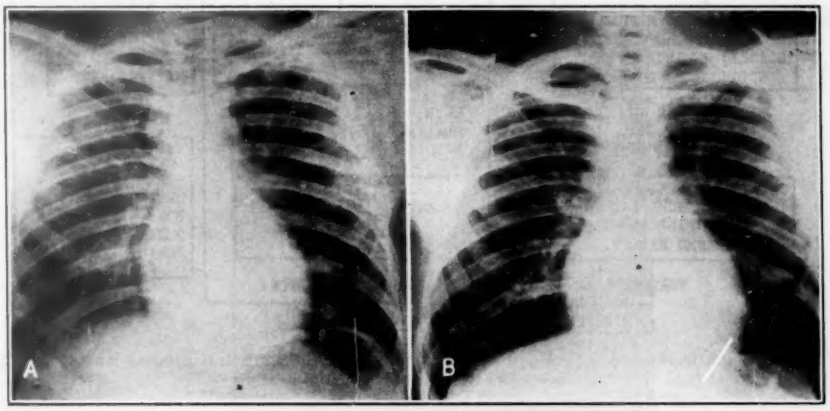

FIG. 3.—*A*, Initial study of Nov. 14, 1942, revealed acute pneumonitis, lateral left mid-lung, right lateral subapical area, right base, and continuous with lower pole of right hilus. Mediastinal adenitis present. *B*, Film 8 months later shows residual cavitation opposite anterior end of 2nd right rib, residual nodule opposite anterior and 7th right rib, with decrease in hilar and mediastinal adenitis. Excavation, nodulation and adenitis were all observed in this 1 patient, with persistence of nodules and cavities for more than 2½ years.

focal necrosis of lung tissue occurs (see Chart 1).

B. *Adenitis.* Hilar and mediastinal adenitis are frequently observed with variable degrees of volumetric increase in soft tissue in these areas. Quite commonly the adenitis becomes more apparent at areas, with subsequent complete return to normal and with no evidence of the disseminated phase at any time.

C. *Cavitation.* In observing patients with this disease one commonly encounters 2 distinct mechanisms of cavity formation (see Chart 1). A pneumonic

lesion may partially resolve, leaving peribronchial infiltration of fibro-exudative appearance, which seems to develop focal necrotic alteration. This type of cavity is ordinarily quite thin-walled and is likely irregular in contour (Figs. 4 and 5). These cavities frequently persist for more than a year and may vacillate in size to the extent of increasing in volume after having decreased markedly. Closure is assumed to occur as a result of predominance of fibrosis over further necrotic alteration and then bronchial occlusion with absorption of air from the interior of the cavity. Once complete closure occurs in a cavity of this type it is rare for it to reappear and ordinarily there is less tendency for appearance of a new area of excavation in the adjacent vicinity than would be true in tuberculosis. Another generalization in connection with cavity formation in coccidioidomycosis is the well-marked tendency for cavitation in areas other than upper lobes in patients with this disease than in those with tuberculosis.

The other mechanism of cavity formation will be further discussed in connection with nodule formation.

An example of an irregular thin-walled cavity, which was regarded as similar to cavitation of coccidioidomycosis, is presented in Figure 6. Despite the similarity of film appearance, serial films and films made prior to entry of this patient into an endemic area revealed that a pulmonary lesion existed before any contact with *Coccidioides immitis* was possible. The nature of the cavity was finally determined by repeated sputum studies and by the appearance of tubercle bacilli at a time when the patient experienced an intercurrent upper respiratory infection.

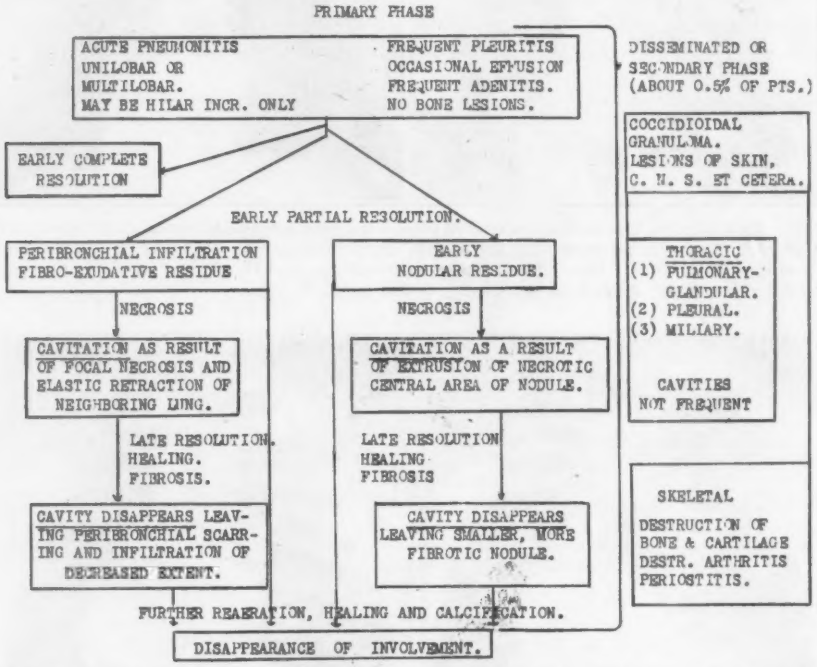

CHART 1.—Schematic representation of possible courses for resolution and progression of coccidioidomycosis as observed roentgenologically.

D. *Nodules.* If sufficient serial films are obtained on patients who have areas of pneumonic infiltration, one will fre-

quently observe nodule formation. These nodules correspond in location to a previously visible patch of pneumonic density of greater volumetric extent. Many of these nodules slowly contract and over a period of months may disappear completely without trace. Other nodules evidently undergo necrosis and with extrusion of the center of such a nodule a cavity appears. A cavity of this type is commonly more nearly round in contour and is likely to have a thick wall (Figs. 7, 8, 9). Cavities which appear in nodules do not ordinarily exceed 1 per patient. Again it is noted that cavities which arise in nodules are frequently encountered in

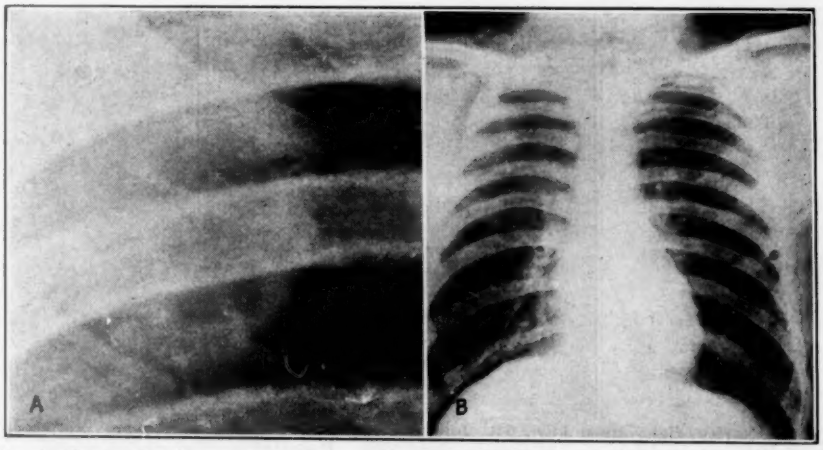

FIG. 4.—*A*, Excavation in area of previous fibro-exudative peribronchial residue. *B*, Same case 7 weeks later. Rapid disappearance of cavity with minimal residual peribronchial accentuation.

FIG. 5.—PA view of cavity in left upper lobe. Cavity known to have been patent for more than 18 months. Variable size of cavity at different times. This is the type of irregular thin-walled excavation which develops in areas of fibro-exudative peribronchial reaction rather than from necrosis of the center of a nodule.

lower lobes and in the right middle lobe, rather than being limited to upper lobes. The appearance of cavitation in coccidioidomycotic nodules which otherwise closely resemble metastatic neoplastic lesions may be cited as a differential diagnostic feature (see Fig. 9). In non-excavating nodules there is often no film indication of etiology and no method for positive exclusion of metastatic carcinoma. Since these nodules have been observed to persist for more than $2\frac{1}{2}$ years, as in the example shown in Figure 3, it seems certain that they will be observed in connection with planned mass surveys of chests to be accomplished in the coming years. A history of exposure to *Coccidioides immitis* and a positive coccidioidin

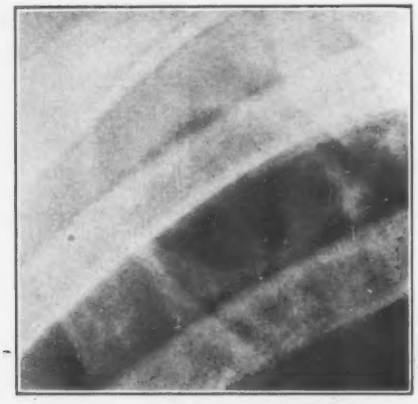

FIG. 6.—Cavity, right upper lobe, with minimal reaction. Onset of pulmonary symptoms before entry of patient to endemic area of coccidioidomycosis. Repeated sputum studies revealed acid-fast organisms.

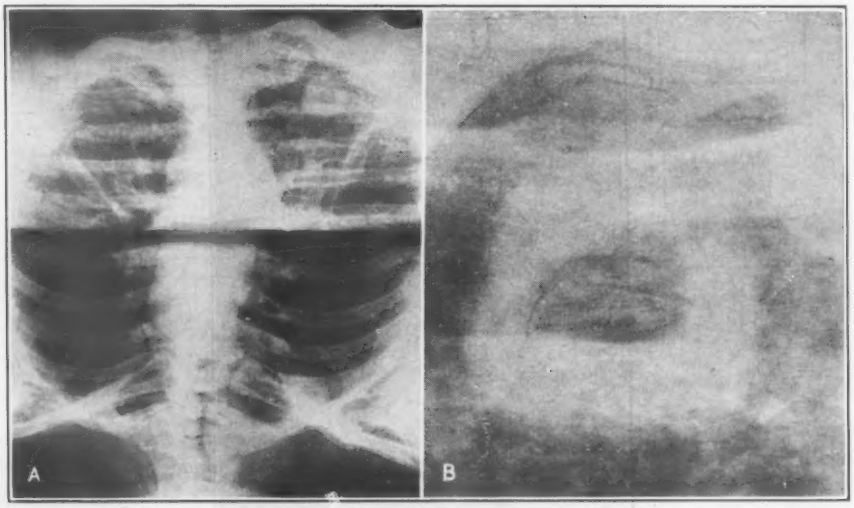

FIG. 7.—*A*, Large nodular lesion, with central excavation. "Doughnut" type cavity; split film, lordotic apical views in AP and PA positions. *B*, Enlarged view of cavity. Center of nodule no longer excavated 11 months later; size of nodule markedly reduced, indicative of predominance of healing and fibrosis over further necrosis.

skin test in such patients may serve as a practical sorting routine in rounded or nodular soft tissue densities detected in lungs of patients who have been in endemic areas, and thus avoid unnecessary hospitalization and diagnostic procedures.

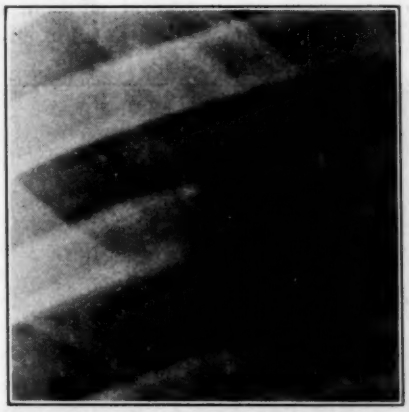

FIG. 8.—View of cavity in right upper lobe. Same patient as Figure 3. Patency of cavity for more than 2½ years observed in serial films.

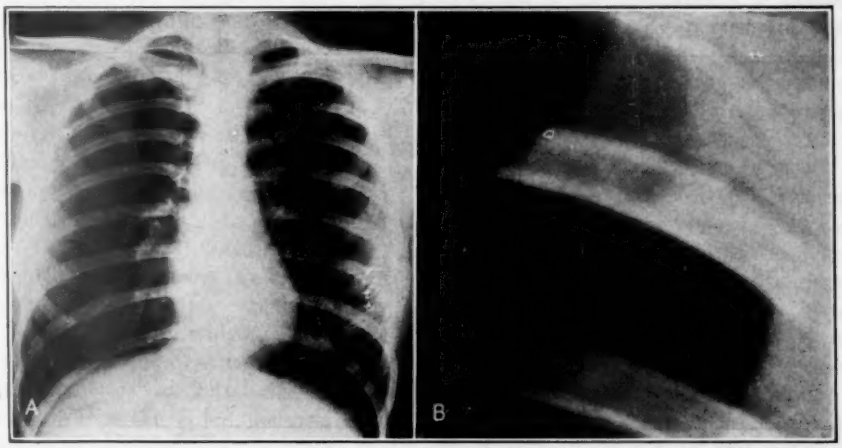

FIG. 9.—*A*, Nodule in lateral subapical region. Clinical signs of active coccidioidomycosis. *B*, Detail view to show excavation in nodule. One year later this patient, a female age 24, was found to have a scirrhous carcinoma of the stomach. Excavation in center of pulmonary nodule and positive clinical findings of coccidioidomycosis aid in excluding the possibility of a metastatic neoplastic lesion.

One frequently observes a characteristic central calcific stippling in soft tissue nodules of coccidioidomycotic origin (Fig. 10). This phase of nodulation indicates well-advanced fibrosis and good progress toward healing. Such deposition of calcium in a soft tissue nodular lesion of the chest would be an exceptional finding in malignant metastatic foci. A similar phenomenon can occur in osteogenic sarcoma metastatic to the lungs, but calcium formed in such metastases is likely to be evenly distributed character throughout the metastatic nodule, while in coccidioidomycosis the calcium is more stippled

in appearance and more likely confined to the center of the nodule.

Cavity closure following necrosis of the center of a nodule appears to come about by a predominance of healing and fibrosis over further necrosis and concentric constriction of the cavity to form a nodule of smaller size than the original one, or bronchial occlusion with absorption of air content, or both.

E. *Pleuritis.* Diffuse pleural thickening, associated with acute pneumonic lesions of coccidioidomycosis is a common finding. The pleural reaction of the primary phase ordinarily subsides during the early days or weeks of the illness. As indicated in Table 1, effusions are quite uncommon. This statement refers to effusion detectable on a routine chest film. Rigos,[15] in reporting a roentgenographic study of pleural effusion, called attention to the fact that an effusion of approximately 400 cc. or less may be present without producing significant alteration in film appearance on a standard 14 x 17 inch chest film made with the patient erect, so that small degrees of effusion may well occur more frequently than indicated in Table 1. Pleural reaction with effusion is represented in Figure 1.

FIG. 10.—Characteristic pattern of central calcific deposition, as observed in some of the pulmonary nodules of coccidioidomycosis as healing progresses. Note non-calcified soft tissue periphery.

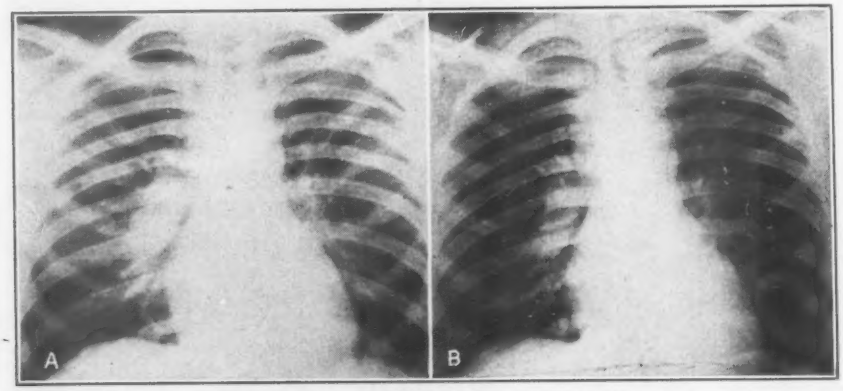

FIG. 11.—*A*, Hilar and mediastinal glandular involvement in colored patient, with disseminated coccidioidomycosis and extensive peripheral adenitis. Granulomatous lesions were present in the skin. *B*, Persistent mediastinal adenitis 6½ months later. Increased density, left supraclavicular area, from peripheral lymph node enlargement. No evidence of pulmonary cavitation.

Progressive or Disseminated Coccidioidomycosis. About 0.5% of patients who acquire clinical primary coccidioidomycosis eventually develop the progressive or disseminating type of infection. This percentage level is directly proportional to the number of racially predisposed individuals in the group considered. Obviously if a large percentage of exposed population is of the Negro race, the incidence of disseminated coccidioidomycosis will be much greater. Nodules, cavities and adenitis of the late primary phase are not to be confused with the disseminated phase of this disease.

A. *Lungs.* In the disseminated phase thoracic lesions may be predominantly hilar and mediastinal adenitis, as shown in Figure 11. Disseminated involvement in this patient (Case 2) was manifested by peripheral adenitis and granulomatous skin lesions and draining sinuses. A miliary distribution of lesions may occur, closely simulating miliary tuberculosis of the lungs. In disseminated cases, pleural reaction may be a predominant feature (Case 3).

B. *Bones.* Coccidioidomycotic skeletal involvement is likely to appear in multiple bones with the probability of associated multiple joint lesions. Lesions are primarily destructive, involving bone and cartilage and producing an appearance similar to tuberculosis. Benninghoven and Miller,[2] in reviewing 500 reported instances of bone and joint lesions due to *Coccidioides immitis*, found the greatest involvement in the spine, pelvis, hands and lower extremities.

C. *Central Nervous System.* Meningitis as a result of coccidioidomycosis is a common occurrence if dissemination does occur. Martin[12] has suggested that meningeal and spinal cord lesions may be more effectively evaluated by ventriculography and myelography respectively.

Roentgenologic features to be emphasized as a result of the present study include the following:

1. From roentgenographic point of view the differential diagnosis of coccidioidomycosis is not limited to tuberculosis. Early lesions may simulate many acute pneumonic processes. Late lesions may simulate various forms of neoplastic disease.

2. Serial film studies of patients with coccidioidomycosis frequently aid in identification of this condition when one bears in mind the 5 common patterns of progression and resolution presented here schematically.

3. Hilar and mediastinal adenitis of considerable extent may occur in the primary phase of coccidioidomycosis, with gradual spontaneous disappearance and without entry of the patient into the disseminated phase.

4. Two distinct mechanisms of cavity formation are prevalent in coccidioidomycosis during the primary phase. Cavitation is relatively less frequent during the disseminated phase.

5. Coccidioidomycotic cavities and nodules not uncommonly persist for many months or several years and must be included in the differential diagnosis of such lesions to be encountered in the planned mass surveys of the chest.

Diagnosis of Coccidioidomycosis. In endemic regions the possibility of coccidioidomycosis is always present, and there has been a tendency to make the diagnosis on insufficient grounds. Too frequently a patient with or without a respiratory infection but a positive coccidioidin cutaneous test has been so diagnosed without cultural or serologic confirmation. A diagnosis on such evidence is always questionable. On the other hand, acute primary coccidioidomycosis acquired in an endemic area but manifested elsewhere will, in all probability, be incorrectly diagnosed. If the late residual pulmonary lesions are unrecognized or misinterpreted, the likelihood of serious error in diagnosis, prognosis and treatment is great. Considering the differential diagnostic possibilities presented by pulmonary nodules or cavitation, especially metastatic malignancy and pulmonary tuberculosis, such errors may be personally, professionally

and economically disastrous. The disseminated form may be confusing if one is unfamiliar with its protean manifestations.

Absolute proof of coccidioidal infection depends upon tissue, cultural and animal inoculation studies. It requires: (1) observation of the characteristic doubly contoured, non-budding endosporulating spherules in tissue sections, sputum, pus, pleural or spinal fluid; (2) recovery of the mycelial form from culture on Sabouraud's or differential media; and (3) demonstration of the spherules in inoculated animals. For the latter purpose, injection into a mouse or guinea pig is made, usually intraperitoneally. Direct smears are not reliable. Gastric washings or bronchoscopy may afford material for examination. When gastric washings are used, examination must be done promptly as the spherules are digested by the gastric secretion.

For practical purposes, positive identification of the fungus obtained by the above procedures is rarely necessary and may be difficult or even impossible in acute primary coccidioidomycosis, in which more often than not the fungus cannot be demonstrated. In such cases, sputum may be entirely lacking, and there are no accessible lesions to afford a source of recovery of the fungus. A diagnosis in the acute phase can be made with reasonable certainty and minimal error if the following criteria are fulfilled: (1) recent residence in an endemic region; (2) an acute respiratory infection with or without erythematous cutaneous lesions; (3) a positive coccidioidin cutaneous test; and (4) a positive coccidioidin serologic test. Additional evidence may be afforded by roentgenologic findings. An initially negative cutaneous test with a subsequent positive test is conclusive evidence of coccidioidal infection. The additional finding of eosinophilia increases the probability of coccidioidomycosis.

Cutaneous Coccidioidin Test. This test has been of great value in the diagnosis of coccidioidal infection. Material for the test was provided by Dr. C. E. Smith of the Department of Public Health and Preventive Medicine, Stanford University. The technique and precautions have been fully described by a number of writers.[5,7,19] A dilution of 1 to 1000 was originally used by us for routine testing. However, it became apparent that the use of this dilution resulted in missing some infections positive in 1 to 100 dilution. Thereafter, the latter was used routinely except in patients exhibiting erythema nodosum. Such patients are hypersensitive to coccidioidin, and in some instances respond with violent local and even systemic reactions. Occasionally 1 to 10 dilution is indicated if disseminated coccidioidal infection is suspected. There is no evidence that reactivation of old focalized lesions or dissemination can occur as a result of the coccidioidin cutaneous test.[7] The test may be negative in early primary coccidioidal infection, but upon repetition will almost invariably become positive in undisseminated cases. It is important to consider the time element between the onset of the disease and the time at which the coccidioidin cutaneous test is performed. If done too early and not repeated, one may acquire the false impression that coccidioidal infection has been excluded. On the other hand, an initial negative test followed by a subsequent positive test is practically conclusive evidence of coccidioidal infection. In 11 of our cases the test was negative on admission and did not become positive until from 2 to 3 weeks later. The test may be negative in disseminated coccidioidomycosis. This was true in 3 of our disseminated cases. In these it remained negative even in 1 to 10 dilution throughout the entire period of observation despite clinical, serologic and cultural evidence of the disease. This is a fact of considerable diagnostic importance as a negative test may be indicative of anergy and not of the absence of coccidioidal infection. A positive test has the same diagnostic significance and limitations as the tuberculin test. It is not acceptable evidence of active coccidioidal infection.

Usually sensitivity to coccidioidin exists indefinitely. However, it is said to diminish or even gradually disappear in some individuals.[7] We have no evidence upon this point. There is some evidence that cross-sensitivity to coccidioidin may exist. Emmons[10] found this to be the case with *Haplospoangium parvum*, a fungus prevalent in parts of Arizona. Smith[19] states that some individuals from Missouri, Illinois, Michigan, Indiana, Tennessee, Kentucky, Ohio, the Virginias, Pennsylvania and New York in which coccidioidomycosis is not known to be endemic show some borderline sensitivity to coccidioidin. However, from a practical clinical standpoint, the test is specific and quite reliable. A positive cutaneous reaction indicates permanent immunity to exogenous reinfection. The skin test is of importance in the presence of pulmonary cavities with negative serologic evidence. In such instances, however, only the recovery of the organisms is decisive. The diagnosis of coccidioidal cavitation can only be presumptive in the presence of a positive coccidioidin cutaneous test but with negative cultural findings.

Coccidioidin Serologic Test. Precipitin and complement fixation tests, as performed by Dr. C. E. Smith, using coccidioidin as antigen, are of value in the diagnosis and prognosis of coccidioidal infections. Obtaining antigen which is consistently satisfactory for complement fixation has delayed publication of these procedures.[19] In mild infections and in the late quiescent or inactive phases, these tests are usually negative. In the active phase of coccidioidal infection they are positive, and the more severe the infection, the more likely it is that precipitins and complement fixing antibodies will develop. In the ordinary, uncomplicated infections precipitins are present in higher titer than complement fixing antibodies and tend to disappear earlier. The titer of complement fixing antibodies parallels the severity of the infection, and in certain ranges is indicative of impending or actual dissemination. Thus, the serologic test provides a reliable index of the severity of the infection, and to this extent has prognostic as well as diagnostic value. A diagnosis of dissemination should not be made in the absence of specific antibodies in relatively high titer.[7] In late, inactive phases of coccidioidal infection, characterized by residual pulmonary cavitation or nodular focalization, the serologic tests have been uniformly negative in our experience even when the fungus could be recovered from the sputum. Serologic tests should be performed whenever dissemination is suspected, regardless of the results of the cutaneous coccidioidin test.

Five patients in our series had clinical, serologic or cultural evidence of dissemination. Two (a 35 year old white private, and a 30 year old colored private) died in from 4 to 5 months. Necropsy, in both instances, revealed miliary dissemination in the lungs, tracheobronchial lymph glands, liver, spleen and kidneys and indolent cutaneous abscesses and verrucous skin granulomata. One case in addition had involvement of the meninges, left ulna, tibia, and knee joint. The clinical and gross pathologic findings in these patients were practically indistinguishable from miliary tuberculosis.

Three disseminated cases recovered. The dominant clinical pattern (namely, meningeal, pulmonary-glandular and pleural) was different in each and likewise differed from the generalized, miliary type which characterized the two fatal cases. For this reason it is felt that a brief clinical summary of these cases will serve to emphasize: (1) the protean features of disseminated coccidioidomycosis, (2) the possibility of recovery in even the most critically ill; (3) and the utter fallacy of evaluating therapeutic measures in individual cases.

Case Report. CASE 1. A 31 year old Negro private entered the hospital Feb. 9, 1943, because of a non-productive cough of 2 weeks duration. Physical examination was negative except for crepitant râles at the right lung base. He had lost 16 pounds in the

2 months prior to admission. A roentgenogram of the chest revealed widening of the right hilar region and irregular mottled density in the right lower lung field, interpreted as probable atypical pneumonia. The day following admission, he developed fever, ranging from 101° to 103° and continuing for 1 month. On Feb. 11, 2 days after admission, the coccidioidin cutaneous test was + in 1 to 100 dilution. On February 14, the leukocyte count was 10,300 with 10% eosinophils. The Kahn test was negative. On February 21, blood obtained from the patient for coccidioidin serologic test was sent to Dr. C. E. Smith at Stanford University School of Medicine. The test was reported as follows:

Complement fixation: serial dilutions of serum (0.25 cc.): 1 to 2, 4+; 1 to 4, 4+; 1 to 8, 4+; 1 to 16, +; 1 to 32, +.

Precipitin tests: serial dilutions of antigens: undiluted, 4+; 1 to 10, 4+; 1 to 40, +; 1 to 100, 0.

These findings were characteristic of severe coccidioidal infection. On March 12, the density in the right lung field was not appreciably changed but there was marked enlargement of the mediastinal shadow indicative of right hilar adenopathy. At this time, the fever subsided and the patient was generally improved. On March 20, the second coccidioidin serologic test, performed at Stanford, was reported as follows:

Complement fixation: serial dilutions of serum (0.25 cc.): 1 to 2, 4+; 1 to 4, 4+; 1 to 8, 4+; 1 to 16, 4+; 1 to 32, 4+; 1 to 64, 3+; 1 to 12, +; 1 to 156, 0.

Precipitin tests: serial dilutions of antigens: undiluted, 3+; 1 to 10, 3+; 1 to 40, 0; 1 to 100, 0.

The increase in the complement fixation titer was interpreted as indicating dissemination despite the normal temperature and absence of clinical evidence of dissemination. About April 20, 10 weeks after admission to the hospital, the patient suddenly developed severe frontal and occipital headache with nuchal rigidity. The cerebrospinal fluid pressure was moderately elevated (manometric readings were not obtained). The fluid contained 900 cells per c.mm., of which 70% were lymphocytes. Cerebrospinal fluid, Kahn and Wassermann were negative. No organisms were found on smear or culture. Following the onset of meningeal symptoms the patient ran a low-grade fever for 5 days. This subsided without recurrence. About Apr. 25, 1945, the spinal fluid showed 530 cells, of which 83% were lymphocytes and 17% neutrophils. The colloidal gold curve was 5555510000. The patient was afebrile at the time but had severe generalized headache, and the nuchal rigidity persisted. There were no localizing neurologic findings at any time during the period of observation. The ocular fundi were consistently normal and at no time were signs of cerebrospinal fluid block demonstrable. On May 26, 1943, approximately 1 month after the occurrence of his meningeal symptoms he was transferred to William Beaumont General Hospital. At that time headaches were his only complaints. These were described as diffuse and of moderate intensity. They were not incapacitating, and the patient could not be convinced of the necessity for remaining in the hospital. His general condition was good, and he had gained considerably in strength but was still 20 pounds below his average weight. Repeated detailed neurologic examinations did not reveal abnormal findings other than a slight to moderate nuchal rigidity. On June 9, cerebrospinal fluid was examined again at William Beaumont General Hospital, and the following findings were reported: white blood cells, 586 (lymphocytes, 58%; neutrophils, 42%). Globulin was 3+, gold curve 5555543210. At this time the fluid was reported positive for *Coccidioides immitis*, both on direct smear and culture. Guinea pig inoculation, unfortunately, was not done. About June 20, approximately 2 months after dissemination to the meninges, the patient first noticed a slight staggering on walking and transitory diplopia which continued off and on for approximately 1 month. On July 5, the cerebrospinal fluid was again reported posifor *Coccidioides immitis*, both on direct smear and culture. The total cell count was 725 (95% of which were lymphocytes). The colloidal gold curve was 5555555421. At this time the patient complained only of headaches and the inactivity that was forced upon him. He had a rather marked feeling of euphoria and appeared normal. Detailed physical examination revealed no signs of dissemination to other organs. Neurologic examination was repeatedly negative. On September 17, he was transferred to a Veterans Administration Facility. There he was

reported as well-nourished, ambulatory and asymptomatic, and apparently normal in all respects. Physical and neuropsychiatric examinations were again essentially negative. Laboratory findings, including blood count, blood Wassermann, sedimentation rate and sputum examination were normal. Chest Roentgen ray, September 1, showed fibrosis involving the right lower lobe and enlargement of the right hilar glands. The cerebrospinal examination, October 1, was reported negative at this institution. On October 5, the patient was given a pass and failed to return to the hospital. He was discharged "Absent Without Leave." Periodic follow-up of this patient has been obtained. The last report (Aug. 15, 1945) reveals that the patient has remained well, is without complaints and is currently employed as a stevedore in Norfolk, Virginia.

Comment. It may be objected that absolute proof that this patient had coccidioidal meningitis is lacking in that the etiologic agent was not identified by animal inoculation studies. However, the clinical and laboratory evidence supports the diagnosis beyond a reasonable doubt. The diagnosis of disseminated coccidioidomycosis is conclusive, being based upon the following evidence: The patient, a colored man, living in a known endemic region, developed a respiratory infection, characterized by cough, fever, roentgenologic signs of pulmonary infiltration and hilar adenopathy, eosinophilia, coccidioidin skin test positive in 1 to 100 dilution and 2 coccidioidin serologic tests with complement fixing antibodies present in high titer indicative of dissemination. During the course of disseminated coccidioidomycosis the patient developed signs and symptoms of meningitis confirmed by repeated cerebrospinal fluid lymphocytosis, a paretic type of gold curve on 3 examinations (strong corroborative evidence in the absence of syphilis) and organisms identified by direct smear and culture as *Coccidioides immitis.*

The patient's course has been entirely benign, and he remains asymptomatic and in apparently good health. In view of the fact that no authenticated recovery from coccidioidal meningitis has been reported and that survival for long periods occurs and complications incident to cerebrospinal fluid block may be long delayed, the case is presented not as one of recovery, but one with a survival period of 2 years and 7 months and who has long been free from symptoms of any kind.* The patient will be followed from time to time and a report of his future course will be made in a subsequent communication.

CASE 2. A 22 year old Negro private, first class, was admitted to the hospital on Dec. 14, 1943, because of progressive cough and expectoration, profound lassitude, weakness for 2 months, and pain in the chest of 2 days' duration. Physical examination was essentially negative except for fever, diffuse sibilant râles bilaterally, and a small indolent verrucous skin lesion in the anterior midline of the neck. The chest roentgenogram on admission showed marked tracheobronchial lymphadenopathy and extensive bilateral pulmonary infiltration. The erythrocyte count was normal, but there were 15,500 leukocytes with a normal differential count. On December 15, the Kahn test was 3+. On December 19 it was 1+ and on December 31 it was reported as doubtful. Subsequently, reports on the Kahn and Kline tests from 3 different laboratories varied from negative to 1+. After Jan. 7, 1944, the Kline, Kahn and Wassermann tests were repeatedly negative. Spinal fluid examination was negative. The coccidioidin cutaneous test in 1 to 100 and 1 to 10 dilutions were negative repeatedly over a period of 5 months. *Coccidioides immitis* was not recovered from the sputum, but biopsy and culture from the skin lesion on the neck were positive for the fungus. Serologic tests done at Stanford confirmed the diagnosis of disseminated coccidioidomycosis. The patient ran a spiking fever from 101° to 103°

* Dr. C. E. Smith, in a personal communication, cites an instance of proven coccidioidal meningitis with survival for 4 years. During this period, however, the patient continued to have symptoms and ultimately died as a result of internal hydrocephalus, a late sequel of his meningitis. Although the infection apparently was inactive mechanical cerebrospinal fluid block presumably was responsible for the patient's death.

daily until May, and thereafter between 99° and 100° for approximately another 2 months.

In January, he developed a second papillomatous skin lesion about the right nares. This enlarged to approximately the size of a walnut, was dry and irregular, without acute inflammatory reaction, and showed numerous white, punctate areas on the surface. *Coccidioides immitis* was recovered from the lesion. In February, the lymph glands at the posterior angle of the jaw on the right side became enlarged. Subsequently, there was extraordinary swelling, tenderness and fluctuation in the right pre-auricular, submental and bilaterally in the cervical and supraclavicular lymph glands. The latter progressed to abscess formation. These were incised, and for 2 weeks continued to drain a thin, turbid fluid with curd-like material from which *Coccidioides immitis* was cultured. In May, there was a reduction in the fever and gradual regression of the lymphadenopathy, gain in weight and progressive clinical improvement which continued until his transfer to another hospital on July 2. He was discharged from the latter and from the Army on August 3 greatly improved. His clinical improvement could not be correlated with attempts at specific therapy including 3 immunotransfusions and a course of penicillin. It is possible that the latter might have prevented secondary infection of the draining abscesses as these were conspicuously free from pyogenic infection and healed uneventfully.

Comment. The dominant clinical features in this case were the high, irregular fever with gradual subsidence over a period of 7 months, extensive bilateral pulmonary infiltration, extraordinary hilar and cervical and supraclavicular lymphadenitis with abscess formation and drainage in the latter, verrucous skin lesions and a transient positive Kahn test. A positive coccidioidin cutaneous test (even in 1 to 10 dilution) was never obtained on this patient, although the coccidioidin serologic test was positive in high titer, characteristic of dissemination. Although the patient was critically ill and originally given a poor prognosis, his symptoms and findings finally regressed and spontaneous recovery occurred.

CASE 3.—A 31 year old white private entered the hospital on Nov. 20, 1942. He had been in Arizona for 2 months. He gave no history of serious illness, venereal or otherwise. One week prior to admission he developed cough, fever and pleuritic pain in the left side of the chest. Physical examination revealed only crepitant râles at both lung bases. The temperature returned to normal on the 5th day and remained so until December 1. At that time, in addition to cough and chest pain, fever of a high swinging type ranging from 100° to 104° recurred, associated with tachycardia, drenching sweats and clinical and roentgenologic signs of massive left-sided pleural effusion. There was an extreme shift of the mediastinum to the right associated with episodes of distressing dyspnea and cyanosis, relieved by repeated thoracentesis. A leukocytosis between 21,000 and 30,000 was consistently present for 2½ months. Eosinophilia ranged between 10 and 27%. The pleural fluid was serous and varied in specific gravity from 1.019 to 1.024, had a high protein content and contained 500 to 600 cells per c.mm., predominantly lymphocytes. No organisms were recovered from the fluid. Serologic tests for syphilis were of interest. They were reported as follows: November 21, Hahn 4+, Kline 4+; November 26, Kahn 4+, Kline 4+; December 3, Kahn 4+, Kline 4+, Wassermann negative. The cerebrospinal fluid was negative. The patient's condition was critical, and because of the possibility of complicating syphilitic infection, antiluetic treatment was begun and continued for 26 weeks. In the light of subsequent experience it is felt that these serologic tests were of the false biologic type and not indicative of actual syphilitic infection. The coccidioidin cutaneous tests in dilution of 1 to 100, or above, were repeatedly negative. The test in 1 to 10 dilution was slightly positive (+). On Apr. 8, 1943, the coccidioidin serologic test was positive in high titer, indicative of dissemination. Numerous sputum examinations were negative for tubercle bacilli and fungi.

The patient was transferred to Fitzsimons General Hospital on February 12. On April 12, *Coccidioides immitis* was recovered from gastric washings and identified by positive guinea pig inoculation. The patient remained critically ill from Dec. 1, 1942, until early in March 1943, following which

there was a gradual regression of all his symptoms and general clinical improvement. At no time did he have clinical evidence of syphilis. He was given a Medical Disability Discharge on June 21. Reports of examination at a Veterans Administration Facility, Dec. 3, 1943, a year after the onset of his illness, indicated complete recovery. The blood Wassermann at that time was negative. No evidence of pulmonary residue or pleuritis was found clinically or roentgenologically.

Comment. The salient features in this case include fever, cough, pleuritic pain, massive pleural effusion with compression symptoms, high sustained leukocytosis, eosinophilia, positive blood Kahn and Kline tests but negative Wassermann; only slightly positive cutaneous coccidioidin tests in 1 to 10 dilution; coccidioidin serologic tests characteristic of dissemination, and recovery of *Coccidioides immitis* from gastric washings. The patient's illness simulated tuberculous pleurisy with effusion, but presented certain hematologic and serologic features not explicable on such a basis. The etiologic diagnosis was established by the coccidioidin serologic tests and confirmed by animal inoculation studies. No localization of the infection other than pleural could be demonstrated. Unfortunately, premature antiluetic therapy instituted because of the urgency of the situation masked the significance of the positive Kahn and Kline tests. However, subsequent experience with false positive serologic tests in coccidioidomycosis leads us to believe that syphilis was improbable in this patient, and that antiluetic treatment should have been withheld until the problem of coexistent syphilis could be decided by further observation and verification tests.

Differential Diagnosis. The differential diagnosis of coccidioidomycosis would require consideration of a variety of unrelated and dissimilar diseases. Many of these have only a superficial resemblance to certain features of coccidioidomycosis. From a practical, clinical standpoint acute coccidioidomycosis may simulate bronchitis, pleuritis, influenza and the bacterial pneumonias. In our experience the most common differentiation was from primary atypical pneumonia. If, as occasionally happens, the initial cutaneous eruption is prominent, it may dominate the clinical picture for a time and suggest measles, scarlet fever, drug idiosyncrasy or diseases of the erythema group. The association of fever, arthritic pain, erythema nodosum, increased erythrocyte sedimentation rate, pleural involvement and pneumonitis might conceivably be mistaken for rheumatic fever. When eosinophilia is marked, parasitic infestation, trichiniasis and even Loeffler's syndrome might be suspected. Practically, these should rarely if ever cause difficulty.

The disseminated form is more likely to be confusing because of the number and variety of manifestations possible in the respiratory, nervous and skeletal systems and in the skin and lymph glands. It must be differentiated from other mycotic infections and from miliary, pulmonary, meningeal and bone tuberculosis. Localized intracranial granuloma simulating brain tumor has been reported.[18,20] In many instances the residual, pulmonary nodular lesions observed roentgenographically are not easily distinguishable from malignant metastases. A knowledge of the multiplicity of clinical features, of the value and limitations of the cutaneous and serologic tests, and cultural and animal inoculation studies should enable one to establish the diagnosis in the overwhelming majority of cases.

Treatment of Coccidioidomycosis. The object of treatment is to afford the patient the optimum conditions for focalizing his infection. This requires adequate rest, general measures and symptomatic treatment such as are carried out for any patient with an active infection. Such measures should be maintained until the infection has subsided clinically and the pulmonary lesions have regressed completely or become stationary. Prolonged hospitalization may be required. The sedimentation rate affords a reliable index

of activity of the infection. Special caution should be exercised in evaluating activity in dark-skinned patients such as Negroes, Fillipinos and Mexicans, who have a greater susceptibility to infection and a higher incidence of dissemination. Drug treatment is of little importance. Symptomatic use of analgesics such as salicylates, with or without codeine, suffice in the ordinary acute cases.

There is no specific treatment for disseminated coccidioidomycosis. The variety of drugs used in the past, including the more recently tried sulfonamides and penicillin, have proven ineffective. Although some have advocated the use of vaccines, their value is still unestablished. Immuno-transfusions have been carried out, but their therapeutic efficacy is difficult to assess and their specific value is doubtful. Incision and drainage of abscesses with concurrent use of penicillin to minimize secondary infection can be undertaken with impunity. These lesions appear to heal satisfactorily under such circumstances. Surgical removal of fungating or verrucous cutaneous lesions has been done with good results. It is obvious, however, that the removal of such lesions exerts no influence on the fundamental course of the disease.

Treatment of patients with pulmonary cavities is still unsettled. Such patients are apparently immune to dissemination and evidence of local spread of the fungus from cavities to adjacent pulmonary tissue has not been demonstrated. Most cavities ultimately heal spontaneously. There is a difference of opinion as to whether or not active treatment should be used even when the cavities persist for long periods. Patients with such lesions are usually in good health and suffer no apparent ill-effects, except occasional hemoptysis in a small percentage of cases. Conservative measures seem to be the treatment of choice. We have had no experience in the use of pneumothorax, phrenicolysis or the application of weighted bags to the chest as suggested by Denenholz and Cheney.[7] We have encountered no patients in whom it was felt that any of these measures were indicated.

Summary. As with many diseases which hitherto have been of merely local or academic interest, coccidioidomycosis, due to the exigencies of war, has acquired a more general and practical clinical importance. A large influx of soldiers and civilians into endemic regions had occurred. Several such areas have been and will continue to be popular health and winter resorts, attracting patients and tourists from various sections of the country. A number of non-immune new arrivals dependent upon their length of residence, inevitably acquire the infection and subsequently move elsewhere. Many such individuals, with or without a history of primary infection show residual pulmonary lesions roentgenographically. The interpretation of such lesions presents considerable difficulty and possibilities for serious error if their nature and significance are unknown. The necessity and responsibility for recognizing coccidioidomycosis in its various phases and wherever encountered is evident.

The present report is based upon personal experience with 77 hospitalized cases of coccidioidomycosis and a study of clinical and roentgenographic material upon approximately 200 additional patients observed in southern Arizona between August 1941 and August 1945. The salient clinical, laboratory and roentgenographic features are presented with particular emphasis upon changes and variations peculiar to different types and stages of the disease. The common Roentgen ray patterns of progression and resolution are described. The fact that coccidioidomycotic cavities and nodules may persist for many months or several years is reiterated, and in the future must be taken into consideration in contemplated mass surveys of the chest. The essential criteria for diagnosis, and the relative value and limitations of various diagnostic procedures are indicated. Three case histories, illustrating different clinical pat-

terns of disseminated cocciodioidomycosis, 1 with apparent recovery from coccidioidal meningitis are reported. The differential diagnosis and treatment are discussed.

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REFERENCES

1. ARONSON, J. D., SAYLOR, R. M., and PARR, E. I.: Arch. Path., **34**, 31, 1942.
2. BENNINGHOVEN, C. D., and MILLER, E. R.: Radiology, **38**, 663, 1942.
3. CARTER, R. A.: Radiology, **23**, 1, 1934.
4. CARTER, R. A.: Radiology, **38**, 649, 1942.
5. Coccidioidomycosis Control Program for the Army Air Forces, West. Flying Train. Com., Santa Ana, Calif., Office of Surg. Gen., Mar. 15, 1944.
6. COLBURN, J. R.: Am. J. Roent. and Rad. Ther., **51**, 1, 1944.
7. DENENHOLZ, E. J., and CHENEY, G.: Arch. Int. Med., **74**, 311, 1944.
8. DICKSON, E. C.: Calif. and West. Med., **47**, 151, 1937.
9. DICKSON, E. C., and GIFFORD, M. A.: Arch. Int. Med., **62**, 853, 1938.
10. EMMONS, C. W., and ASHBURN, L. L.: Pub. Health Rep., **57**, 1715, 1942.
11. GIFFORD, M. A.: Ann. Rep., Kern Co. Health Dept. for July 1935 to June 30, 1936.
12. GOLDSTEIN, D. M., and LOUIE, S.: War Med., **4**, 299, 1943.
13. MARTIN, C. L.: Texas State J. Med., **38**, 385, 1942.
14. POSADAS, A.: Ann. Circ. Med. Argentine, **15**, 585, 1892.
15. RIGOS, F. J.: Radiology, **36**, 568, 1941.
16. RIXFORD, E.: Occidental Med. Times, **8**, 704, 1894.
17. ROSENBERG, E. F., DOCKERTY, M. B., and MEYERDING, H. W.: Arch. Int. Med., **69**, 238, 1942.
18. SCHLUMBERGER, H. G.: AM. J. MED. SCI., **209**, 483, 1945.
19. SMITH, C. E.: Med. Clin. North America, **27**, 790, 1943.
20. STORTS, B. P.: J. Am. Med. Assn., **112**, 1334, 1939.
21. WERNICKE, R.: Centralbl. f. Bakt., **12**, 859, 1892.
22. WINN, W. A., and JOHNSTON, G. R.: Ann. Int. Med., **17**, 407, 1942.
23. WINN, W. A.: Arch. Int. Med., **68**, 1179, 1941.

PENICILLIN THERAPY IN PYOGENIC DERMATOSES*

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Pyogenic cocci flourish in diseased epidermis. Since the first report of Roxburgh[3] on the use of penicillin in these superficial infections, many papers have appeared. There is unanimity as to the effectiveness of penicillin in impetigo, ecthyma and furunculosis; but with sycosis and with secondary infections in eczematous eruptions and acne, previous observers report varying degrees of success. Much uncertainty remains also as to dosage and methods.

The following observations were made on 618 soldiers. The more severe cases and others who could be relieved from duty (211 in all) were treated in a hospital, the majority (407) in a dispensary. The lesions were grouped under the following diagnoses (Table 1).

Impetigo. There were 52 cases of impetigo contagiosa involving head and neck and 35 cases of "bullous" or "tropical" impetigo[1] involving chiefly the covered portions of the body, especially the axillæ. The results in both forms were almost uniformly good whether treatment was topical or intramuscular. This agrees with the experience of most previous observers. The rapidity of response was striking. Many cases were much improved overnight, 9 appeared well in 3 days and the median time for clearing was 6 to 7 days.

There were apparent explanations for most of the 16 failures. Three patients had been sensitized to penicillin, 2 of them by previous treatment. Three were treated with ointment containing only 100 units of penicillin per gram. Two had also a folliculitis of the beard, a probable source of reinfection. Others were obviously irregular in applying treatment.

The frequency of relapse was surprising. Of 35 cases recalled for follow-up after 2 weeks, 10 (28%) had developed new lesions. This would appear an indictment of penicillin therapy, but it was doubtless due to the rapidity of apparent cure which led to premature cessation of treatment. It indicates, however, the necessity of continuing treatment of neighboring as well as involved areas after apparent cure. It may prove advisable to follow penicillin with ammoniated mercury or some other antiseptic.

Ecthyma. The ecthymatous lesions encountered varied in extent and severity. Several resulted from chigger bites, others from scabies, creeping eruption or excoriated dermatitis venenata. Few seemed characteristic of the fly-borne ecthymas which were common among combat troops in tropical areas.

Response to local or intramuscular treatment was rapid and, considering the obstinacy of these cases to other therapy, even more impressive than in impetigo. Of the 33 cases treated, 27 (82%) cleared in a median time of 7 days; 17 were fol-

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lowed from 1 to 3 weeks after healing and only 3 (18%) had relapsed. Four of 6 additional cases who disappeared after 1 or 2 days of treatment were already much improved.

Of the 6 failures, 1 appeared sensitized although he disappeared before skin tests could be carried out. A second was treated only with 100 unit gauze and resistant strains of staphylococci were recovered from the remaining 3.

to 3 years duration. Others had developed during an attack of impetigo 1 or 2 weeks before. Some may well have been transitory infections, but some cases of only a weeks duration proved very resistant to treatment.

In several Negro patients, the bearded area was covered with keloid-like papules, a type of lesion which has been variously interpreted.[5] The foreign body effect of embedded hairs was probably the chief

TABLE 1.—RESULTS OF PENICILLIN TREATMENT

Diagnosis	No. cases*	Duration of infection†			Cultures from lesions‡			Infection controlled§	Time in days¶			Relapses observed		Treatment, failures			Reactions to treatment
		Median	Maximum	Minimum	Hemolytic streptococcus	Sensitive staphylococcus	Resistant staphylococcus	% of cases	Median	Maximum	Minimum	Cases followed 2 weeks	Relapsed	Improved	Unimproved	Worse	% of cases
Primary infections					%	%	%						%	%	%	%	
Impetigo contagiosa	52	7	60	2	19	79	38	79	6	26	3	20	32	2	17	2	8
Impetigo bullosa	35	10	1y	1	18	82	45	86	7	17	3	15	20	0	14	0	0
Ecthyma	33	14	102	3	57	36	75	82	7	37	3	17	18	9	6	3	6
Folliculitis of beard	50	49	10y	2	13	57	54	36	15	79	3	10	20	24	26	8	14
Folliculitis elsewhere	28	14	10y	1	4	50	39	29	9	15	3	5	60	14	57	0	7
Furunculosis	21	21	1½y	2	0	73	27	80	7	41	3	10	10	5	15	0	0
Hidrosadenitis	9	14	1y	2	0	86	14	100	7	39	5	2	50	0	0	0	0
Secondary infections in																	
Dermatophytosis of feet	226	..	..	..	62	35	52	82	4	37	1	118	14	8	8	2	4
Intertrigo	15	..	..	..	33	0	92	20	12	18	4	1	0	33	27	20	20
Eczematous dermatitis	144	..	..	..	46	48	75	40	11	80	2	29	38	15	34	11	25
Acne	23	..	..	..	0	12	35	4	47	47	47	1	0	13	79	4	9

* Of the 618 patients, 18 were treated for 2 lesions of different character and each lesion was considered a separate case.

† The median, maximum and minimum duration of infection is tabulated in days, except where a "y" indicates years. It was impossible to determine the duration of secondary infections.

‡ Percentages are based on cases from whom satisfactory cultures were obtained, about 80% of the total. Two or 3 types were frequently obtained from open lesions, simultaneously or at different times during treatment.

§ The infection was recorded as "controlled" when clinical signs of pyogenic infection disappeared. In the primary infections, this record coincided with the disappearance of the lesion, except for residual erythema or desquamation.

¶ "Time" records the median, maximum and minimum days under treatment, before infection was controlled.

FOLLICULITIS OF THE BEARD. It is well known that simple follicular infections of the beard respond well to antiseptic treatment, whereas other cases in which constitutional or anatomic factors or allergy seem to play a dominant rôle are most difficult therapeutic problems. There are, however, no precise criteria by which the latter group, called sycosis barbæ, can be identified. Some have reported success with penicillin therapy in sycosis, but others only temporary benefit or complete failure. The cases of this series were of unequal severity: 8 were of from 2 months

cause of their pustules. Two patients on culture yielded only a few coagulase negative staphylococci and it is doubtful if these eruptions were caused by infection. In others pustules continued to develop after pathogenic cocci could no longer be found in their lesions. One obvious difficulty in treatment was the delivery of an effective dose of penicillin at the depth of the hair follicle. Various combinations of intramuscular and oral therapy with local applications of different strength were employed in hope of achieving success.

The results were not easy to judge on

account of the frequent persistence of scattered macules and papules after active pustulation had ceased. The percentage of cases that could be considered cured was low (Table 1) and follow up periods too short to be certain of the permanence of cure in a disease so prone to relapse.

Apparent cure in 3 to 23 days was obtained in 14 cases. These varied in severity and in duration from a few days to 1 year; 10 of them were followed for 7 to 18 days and 8 showed no evidence of relapse in this brief period.

Cultures from 11 of these successful cases were studied and showed a predominance of penicillin sensitive organisms.

	Cases
Penicillin sensitive staphylococci	3
Penicillin sensitive staphylococci and streptococci	3
Penicillin resistant staphylococci	1
Sensitive cocci and resistant cocci	2
Staphylococci of doubtful sensitivity	1
Only coagulase negative staphylococci	1

It appeared that in folliculitis caused by sensitive cocci, penicillin is effective if applied in sufficient concentration.

In 4 other cases the infection was controlled only after 5 to 11 weeks of treatment. All showed penicillin resistant staphylococci, which persisted in repeated cultures. After trial of many dosages, they finally cleared under paintings with a solution of 100,000 units per cc., plus (in 3 cases) intramuscular injection of 600,000 units a day.

Eight other cases with resistant staphylococci seemed nearly clear after similar huge doses, though occasional pustules continued to appear. Still others showed striking improvement in the 1st week and developed no conspicuous lesions as long as treatment was continued. One must doubt whether any of these patients were permanently cured, but it did appear that enormous amounts of penicillin had some inhibitory effect on these resistant staphylococci.

FOLLICULITIS OF THE TRUNK AND EXTREMITIES. The results in this group of 28 patients were surprisingly poor. Only 8 cleared up, 4 others were markedly improved and 16 made no significant progress. The results of the cultures were also surprising. These eruptions, chiefly on the buttocks, thighs and legs, or in the groin or axillæ appeared to be infections, but often responsible organisms could not be isolated. In 3 cases, some of the hairs pulled from the center of pustules gave no growth when inoculated on blood plates. Other cultures showed only 1 or 2 colonies or only coagulase negative staphylococci. From only 4 did we obtain numerous colonies of penicillin susceptible, coagulase positive staphylococci. One of these cases cleared and 2 improved.

FURUNCULOSIS. Twenty-one cases of furunculosis were treated, 5 by intramuscular injections, 5 by oral administration, 4 by intramuscular injections followed by oral administration and 7 by local application of ointments. They were treated for 2 distinct purposes: the control of the acute furuncles and the prevention of recurrence. As furuncles discharge and heal spontaneously the percentage healing under penicillin is of no significance, but definite impressions were gained from our observation of these cases.

Local application had no effect except perhaps to accelerate healing of already discharging furuncles. The effect of intramuscular injections was dramatic in 1 case with multiple large furuncles and in 6 others appeared to hasten the involution of acute lesions. Oral treatment gave similar, though less convincing results. Relapses occurred in only 1 of the 10 cases which were followed.

HIDROSADENITIS. Uniform, at least temporary success was obtained in 9 patients with axillary lesions probably originating in the sweat glands. The majority had recent infections, but 1 had had repeated lesions for a year and another for 6 weeks. They received intramuscular injections for from 2 to 10 days, and in

3 cases this was followed by a course of oral therapy. All cleared in a median time of 1 week. Only 2 cases could be followed and 1 of these had relapsed.

DERMATOPHYTOSIS. Among the cases treated in this series were 264 pyogenic infections of the feet, which were apparently secondary to dermatophytosis; 36 cases, who showed an eczematous reaction on the dorsa of the toes, have been included for tabulation in the group of eczematous dermatidides, because it was found that the presence of such reaction influenced the response to penicillin. Of the remaining 226 non-eczematous cases, 25 had lymphangitis or lymphadenitis, which in most arose from infected dermatophytic bullæ on the sole; 42 others had similar infected bullæ without extension of the infection to the lymphatics. There was a non-suppurative cellulitis of the toes in 22 cases. In 78 cases there were weeping areas where the stratum corneum was denuded and 13 showed fissures between or beneath the toes. Of the remaining 46, many showed pustules or other evidence of pyogenic infection, but some were simple intertrigos of the toes, in which it was desired to test the effect of penicillin. Fungi were demonstrated in 73% of 240 cases, scrapings from whom were examined microscopically.

The pyogenic infection appeared controlled in 82% of these cases in a median time of 4 days. The relapse rate 14% was not high. Fissures healed promptly in all 13 cases treated. Denuded areas healed in 78% of such cases in a median time of only 3 days. Cellulitis cleared in the same percentage. Two patients with a streptococcus infection, which spread by undermining the horny layer of the sole—a type of infection it has been difficult to control with other agents—did well under penicillin. The most convincing results were those in cases complicated with lymphangitis and lymphadenitis. It had previously seemed necessary to hospitalize many such cases, but 19 of the 25 cleared up when bandaged with penicillin gauze and simply relieved from active duty.

These results would lead one to conclude that this antibiotic is of outstanding value in these pyogenic infections of the feet; but the bacteriologic findings make it difficult to attribute all cures to the penicillin. Of 165 cases from which cultures were studied, 90 (54%) yielded staphylococci resistant to penicillin *in vitro*. These were sometimes in pure culture, sometimes mixed with penicillin sensitive strains and often with streptococci (see table).

	No. cases	Infection controlled (%)
Penicillin sensitive staphylococci only	21	90
Penicillin resistant staphylococci only	26	73
Penicillin resistant staphylococci with or without sensitive staphylococci and/or hemolytic streptococci	90	78

The following observation showed that the less severe cases would heal without the aid of an antibacterial agent. Nine patients with denuded areas or infected bullæ were treated for 1 to 8 days on 1 foot with penicillin gauze and on the other with gauze impregnated with plain carbowax. In 8, both feet healed with equal rapidity. In the 9th, the penicillin foot healed more rapidly.

It is probable that in cases showing only sensitive cocci, penicillin was effective, and that in others, with mixed cultures, its inhibition of sensitive strains was decisive in controlling the infection. The overall frequency and rapidity of cure was probably increased by the routine use of penicillin.

Comparison with cases previously treated with other antibacterial agents, indicates that penicillin was more effective. During the past 3 years we have used sulfathiazole 5% combined with tannic acid 10%, zinc peroxide 20% and zephiran 0.5% extensively in treatment of pyogenic infections of the feet. Selecting only cases

with similar lesions and only those whose feet were bandaged with carbowax gauze impregnated with the antiseptic, the results were compared with the patients similary treated with penicillin (Table 2).

In all 3 types of cases, the percentage clearing under penicillin was higher and the average time of clearing less than with the other treatment agents. The rapidity of response to penicillin was especially striking. In 3 days infection was controlled in 40% of the cases treated with penicillin, in 20% of those treated with sulfathiazole, in 18% of those treated with zinc peroxide and only 12% of those treated with zephiran.

Table 2.—Secondary Infections in Dermatophytosis

Types of lesions	No. cases	Infection controlled (%)	Average time (days)
Infected bullæ:			
Penicillin	40	85	4
Sulfathiazole	8	62	4½
Zephiran	6	83	3
Denudation:			
Penicillin	78	81	3
Sulfathiazole	61	59	6
Zinc peroxide	28	55	11
Zephiran	8	50	5
Fissures:			
Penicillin	13	100	3
Sulfathiazole	15	67	4
Zinc peroxide	8	75	6
Zephiran	7	57	8

Intertrigo. There were 15 patients with intertrigo of the groin or axillæ treated with penicillin ointments; 8 were examined for fungi and all were negative; infection was controlled in only 3 cases; 5 were materially improved. It is doubtful if even the few cures obtained were due to specific action of the penicillin as out of 12 cases from whom cultures were obtained, 11 showed resistant staphylococci.

Eczematous Dermatitis. Under this heading are included 144 heterogeneous cases all of which showed a dermatitis characterized by edema, and pin-point vesicles or areas of exudation. Most showed also pustulation or other evidence of secondary infection. The etiology of the primary dermatitis was varied and often undetermined, and it was not expected that penicillin would influence it. On culture, however, these cases often yield a growth of coagulase positive staphylococci, more profuse than one obtains from a boil, and it was hoped penicillin would control this secondary infection which seemed frequently the chief cause of symptoms. In this series it appeared promptly effective in only 28 cases in which evidence of pyogenic infection disappeared in from 3 days to 2 weeks. These included 11 cases of probable dermatophytosis with secondary infection and eczematization, 5 eczematous eruptions on the hands and 5 on the lower legs and ankles which may have been primarily dermatophytids. There were 4 cases of contact dermatitis in which protection from the respective allergens doubtless aided in curing the infection. The effect of penicillin was most convincing in 3 cases of infectious eczematoid dermatitis of the toes secondary to paronychia which cleared up promptly and completely.

There were also 10 cases of chronic dermatitis of the hands, feet or lower legs from 1 month to 7 years in duration in which not only suppuration, but practically all signs of dermatitis cleared up under prolonged treatment with penicillin. Two were sensitive to shoe leather, but removal of shoes had not sufficed to clear up their infection. This small group of

therapeutic successes appeared important on account of the difficulty of aiding these chronic cases by any other procedure.

Individualization of treatment seemed necessary. Some, who reacted to strong ointment, did well under a weaker preparation. Others unimproved by weak ointments, cleared up under the use of a stronger. Some who appeared sensitized at first, could later be treated successfully after their sensitization had subsided. In several cases, the infection was finally controlled only after trying many modifications in therapy for a period of 1 or 2 months, and 1 was treated 11 weeks. Two patients who had repeatedly reacted to attempts at local therapy finally cleared up without evidence of sensitization under intramuscular injections. Conversely, 1 patient who reacted with urticaria to intramuscular injections, was successfully treated with local applications.

In only 2 out of 12 cases of seborrheic dermatitis was penicillin therapy followed by significant improvement. In a number of other eczematized cases pustulation was controlled without material relief of the patient's discomfort. In the majority, even the pyogenic infection proved resistant. This is probably explained by the frequent occurrence of penicillin resistant strains of staphylococcus and the frequency with which hypersensitivity to penicillin develops in these eczematized cases.

Acne. Pustular or cystic acne was treated in 23 cases, again with no expectation of influencing the primary disease, but in hope of controlling the secondary infection. In only 1 case did the infection appear completely controlled. Local applications of ointment had no discernible effect in 4 cases. Intramuscular injections or oral treatment showed substantial improvement in only 3. This may well be explained by the fact that cultures from 6 cases showed resistant strains of staphylococci, and that cultures from 1 cystic case were completely sterile except for a few colonies of coagulase negative staphylococci.

The temporary successes with penicillin therapy, though few, were of some interest because incision of infected cystic lesions frequently leaves scars which are disfiguring when they occur on the face. The possibility of controlling such lesions without incision would seem a therapeutic asset, even if success is infrequent and temporary.

Miscellaneous Cases. A number of patients with other dermatoses which appeared secondarily infected were treated with penicillin ointment. Among them were found 4 cases of psoriasis and 4 of lichen simplex. In 1 of these latter and 1 patient with pustular rosacea, from whom streptococci Type C were recovered, the infection cleared promptly. Most of the others from whom cultures were obtained yielded only resistant strains of staphylococci and all failed to clear under treatment.

The Susceptibility to Penicillin of Strains Encountered. Strains of pyogenic cocci isolated from these lesions were tested for their sensitivity to penicillin by a cylinder plate method.[6] Most staphylococci fell into 2 groups and gave readings indicating either inhibition by 0.01 unit of penicillin or less per cc. or resistance to 100 or more units. Only a moderate number of intermediate strains were encountered. Only beta hemolytic streptococci were recorded and most were highly sensitive to penicillin. Many were of Group A, but strains of Group C and Group G were frequent and a few of Group B were isolated. The pathogenicity of the last 3 must be questioned.

Streptococci disappeared in most cases after a few days of local penicillin treatment, but occasionally reappeared in later cultures although treatment was continued. In a few cases they persisted and 1 eczema of the ankle yielded a profuse growth of penicillin sensitive streptococci (Group C) in 10 successive cultures during a 3 weeks period of local treatment. Sensitive strains of staphylococci also disappeared in most cases though with less regularity and speed. Resistant

strains of staphylococci often persisted after treatment even with concentrated solutions, but usually disappeared if the lesions healed.

The overall correlation between the response of different diseases to treatment and the sensitivity to penicillin of organisms isolated from them was good except in ecthyma and dermatophytosis. In impetigo, furunculosis and hidrosadenitis the percentages of susceptible cocci and of favorable response to treatment were high. In folliculitis, intertrigo, eczematous dermatitis and acne resistant strains were frequent and response to penicillin therapy was poor. In ecthyma and in infections secondary to dermatophytosis, however, the clinical results were excellent although the percentage of resistant strains was high. Of 14 patients with lymphangitis or lymphadenitis from whose portal lesions resistant strains of staphylococci were isolated, 11 recovered promptly under penicillin. In nearly all groups, individual cases from which resistant strains were recovered healed promptly.

Three events might account for these paradoxical results: (*a*) Healing may have been spontaneous or due to non-specific effects of the dressings supplied. This was probably true in many cases of dermatophytosis. (*b*) Inhibition of penicillin sensitive strains may have determined the cure because the coincident resistant strains were less virulent. Inhibition of the streptococci frequently present in ecthyma and dermatophytosis was probably decisive and it appeared in many cases that inhibition of sensitive staphylococci resulted in cure in spite of persistence or resistant strains. The observations of Spink,[9] however, throw doubt on the latter hypothesis. (*c*) Strong ointment or large doses may have produced sufficient concentrations in some lesions to inhibit resistant strains. This could hardly be true of some strains which were viable in broth containing 1000 or 10,000 units per cc., unless one assumes that penicillin is more effective in tissue than in test tube. However, clinical observation did strongly suggest that penicillin was effective against resistant staphylococci especially in some cases of folliculitis of the beard, which finally cleared after most intensive therapy.

Sensitization to Penicillin. Reactions during treatment (Table 1) or to subsequent patch or intradermal tests showed that penicillin is a potent skin sensitizer. Some form of cutaneous reaction which appeared allergic appeared in 11% of all patients and in 25% of those with eczematous dermatitis. These will be discussed in a subsequent report.[3] Although many of these sensitizations were localized and transitory, they accounted for a large proportion of the treatment failures. In the brief treatment required for impetigo, ecthyma or infected dermatophytosis they seldom interfered with success but their high frequency in cases with previous eczematization seemed a warning against the local application of penicillin in such cases.

Local Treatment. Ointments containing 100,000 and 10,000 units per gm. were freshly prepared each week in 3 types of bases, an oil in water emulsion (U. S. Army Supply Item No. 1173800), a bentonite gel and a glycol-carbowax mixture.[2] A solution of 100,000 units per cc. of water was painted on certain lesions. Ointments were kept on ice and reapplied every 2 hours when practicable. Gauze impregnated with penicillin in carbowax base was found convenient and economical for cases requiring dressings.

The 100 unit ointments were definitely less effective than the stronger preparations. In a few cases infection was controlled by 10,000 unit or 100,000 unit applications after the weaker ones had failed. On the other hand, sensitization developed more frequently after use of the stronger preparations. Although evidence for greater effectiveness of the stronger preparations was inconclusive, it seemed probable that ointments containing 10,000 units per gm. were advantageous in most instances and painting with 100,000 units necessary in some cases of folliculitis.

No difference in the bacteriostatic effect

of penicillin could be detected when applied in the 3 bases. The emulsion base was best tolerated by eczematous cases and carbowax proved most convenient for dressings. There is also evidence that penicillin is more stable in carbowax because it is anhydrous.[4]

INTRAMUSCULAR THERAPY. Penicillin in oil and beeswax was injected once or twice daily in doses of 300,000 units. Four cases of impetigo and 3 of ecthyma were so treated, enough to demonstrate that parenteral penicillin was effective in these superficial infections. Such treatment seemed quite unnecessary. While some cases of folliculitis of the beard did well with strong local applications, others failed to respond until given intramuscular injections. Most of our cases of lymphangitis and cellulitis responded to application of penicillin to the portal of entry, but parenteral therapy was obviously more effective. In furunculosis and hidrosadenitis, parenteral or oral, seemed the only routes of therapy worth trial. The frequency of sensitization following local treatment of eczematous dermatitis indicated that in the majority of these cases only systemic therapy should be used.

ORAL THERAPY. Penicillin was administered orally every 2 hours for 9 doses, to total 550,000 or 1,100,000 units daily. The results were inconclusive. For reasons which we could not determine, erratic and generally unsatisfactory blood levels were observed in most cases. This may have been because our patients were ambulant and on a heavy diet or possibly because the formalin treated capsules[7] employed in most of our cases failed to release penicillin in the upper intestine. In spite of these low blood levels, 1 impetigo, 1 folliculitis of the beard and 4 of 5 cases of furunculosis cleared after taking capsules. Oral therapy seemed effective as a sequel to intramuscular in the few cases of chronic furunculosis, folliculitis and hidrosadenitis in which prolonged follow-up treatment could be maintained. If reduced costs make the huge doses required practicable penicillin by mouth should prove useful in suppressive treatment for prevention of relapse in these chronic infections. Its use in eczematous dermatitis would greatly reduce the danger of sensitization. It may even prove more convenient than ointments in treating superficial infections such as impetigo.

Summary. 1. Local penicillin therapy was rapidly effective in the majority of cases of impetigo, ecthyma and the pyogenic complications of dermatophytosis.

2. Intramuscular penicillin was effective in furunculosis and hidrosadenitis.

3. One-third of our cases of folliculitis of the beard cleared at least temporarily under penicillin. Concentrated local applications combined with intramuscular injections often appeared necessary.

4. Secondary infections in eczematous dermatitis were controlled in 40% of cases, but sensitization developed frequently after local therapy.

5. Penicillin was seldom effective in seborrheic dermatitis, intertrigo, folliculitis of the trunk or extremities or acne.

REFERENCES

1. D'AVANZO, C. S.: Impetigo Bullosa in the Tropics, Arch. Dermat. and Syph., **52**, 28, 1945.
2. HOPKINS, J. G.: Some Newer Bases for Use in Cutaneous Therapy, J. Investig. Derm., **7**, 171, 1946.
3. HOPKINS, J. G., and LAWRENCE, H.: Sensitization to Penicillin, J. Allergy (in press).
4. MELENEY, F. E.: Personal communication.
5. PINKUS, H.: Chronic Scarring Folliculitis, Arch. Dermat. and Syph., **51**, 173, 1945.
6. REBELL, G. C.: Occurrence of Staphylococci and Hemolytic Streptococci on Normal Skin and in Dermatoses of the Feet (in press).
7. ROSS, S., BURKE, F. G., and MCLENDON, P. A.: Penicillin by Mouth, J. Am. Med. Assn., **129**, 327, 1945.
8. ROXBURGH, I. A., CHRISTIE, R. V., and ROXBURGH, A. C.: Penicillin in Treatment of Certain Diseases of the Skin, Brit. Med. J., **1**, 524, 1944.
9. SPINK, W. W., HALL, W. H., and FERRIS, V.: Clinical Significance of Staphylococci, J. Am. Med. Assn., **128**, 555, 1945.

ELECTROCARDIOGRAPHIC PHENOMENA ASSOCIATED WITH SPONTANEOUS PNEUMOTHORAX AND MEDIASTINAL EMPHYSEMA

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In the differential diagnosis of acute, severe precordial pain, spontaneous pneumothorax alone or in association with mediastinal emphysema must be considered. The literature[1,4,10,11,13,14] contains descriptions of a fair number of such cases and in the course of extensive hospital practice instances of spontaneous pneumothorax are not rare. There are sufficient physical signs, for the most part, to render the diagnosis readily apparent. In some instances, however, the amount of air escaping into the pleural space is small and the diagnosis can only be made by radiography. In a similar manner, although Hamman's sign is generally present in mediastinal emphysema, it often simulates a pericardial fraction rub. When this is associated with electrocardiographic changes, substernal oppression and radiation of pain to the neck or to the arms, one may well consider the case to be one of myocardial infarction. Pneumothorax alone is known to produce minor changes in the electrocardiograms.[2,8,9] These are concerned largely with rotation of the electrical axis, diminution in the height of the T waves and slight displacement of the ST segments. On the other hand, pneumothorax with mediastinal emphysema may, apparently, result in grossly abnormal electrocardiographic tracings.[10,11] Miller[11] has reported a series of such cases which demonstrated a low T1, flat or inverted T4 (4F) with elevation of the ST segment and small or absent initial deflection in the 4th lead. He suggested that these findings were probably the result of the associated pneumothorax. However, he also considered the presence of a temporary functional coronary insufficiency. This was felt to result from right heart stasis inducing resistance to coronary emptying. This in turn is due to compression of the pulmonary vessels and reduction of their lumen by air dissection of the vascular sheaths.[8] Interference with coronary filling is also thought to occur as the result of increased mediastinal pressure. The latter would be similar in effect to increased intrapericardial pressure and could even cause tamponade of the heart. Other observers[8] have noted that rotation of the heart on its anatomic axis may result in electrocardiographic alterations. Any or all of these factors may be operative. It is of interest to note that these cases demonstrating gross electrocardiographic changes were all associated with a left-sided pneumothorax.

It is the subject of this paper to inquire further into the causes of electrocardiographic abnormalities encountered in the presence of spontaneous pneumothorax occurring together with mediastinal emphysema.

Case Reports. Case 1. An 18 year old soldier came into the hospital complaining of severe substernal pain which radiated to the neck and shoulders. The admission diagnosis was coronary thrombosis. The pain occurred suddenly some 2 hours earlier while patient was reaching for a telephone. It became progressively more severe and required morphine for control. The patient volunteered the information that he felt more comfortable in the erect position. The past and family history was entirely non-contributory.

When first seen the patient was pale and sweating and appeared to be in moderate shock. The pulse was 96 and of good quality. The temperature was 97.8 and the blood pressure 120/76. Examination of the lungs revealed no gross abnormalities and the heart was remarkable only in that it was percussed with difficulty and that the sounds were distant. Due to the patient's condition the examination was carried out in the supine position.

An electrocardiogram was made at once and this demonstrated a somewhat low T1, a slightly inverted T4 (4F) and an absent R4. At this time the patient was reëxamined and in the erect position the characteristic mediastinal crunch was noted; the heart sounds were louder and the left border could be percussed without difficulty. A Roentgen ray of the chest confirmed the impression of spontaneous pneumothorax on the left side. There was an estimated 10% collapse of the lung. Lateral views were interpreted as demonstrating air in the mediastinum.

On the following day extensive electrocardiographic studies were made. These

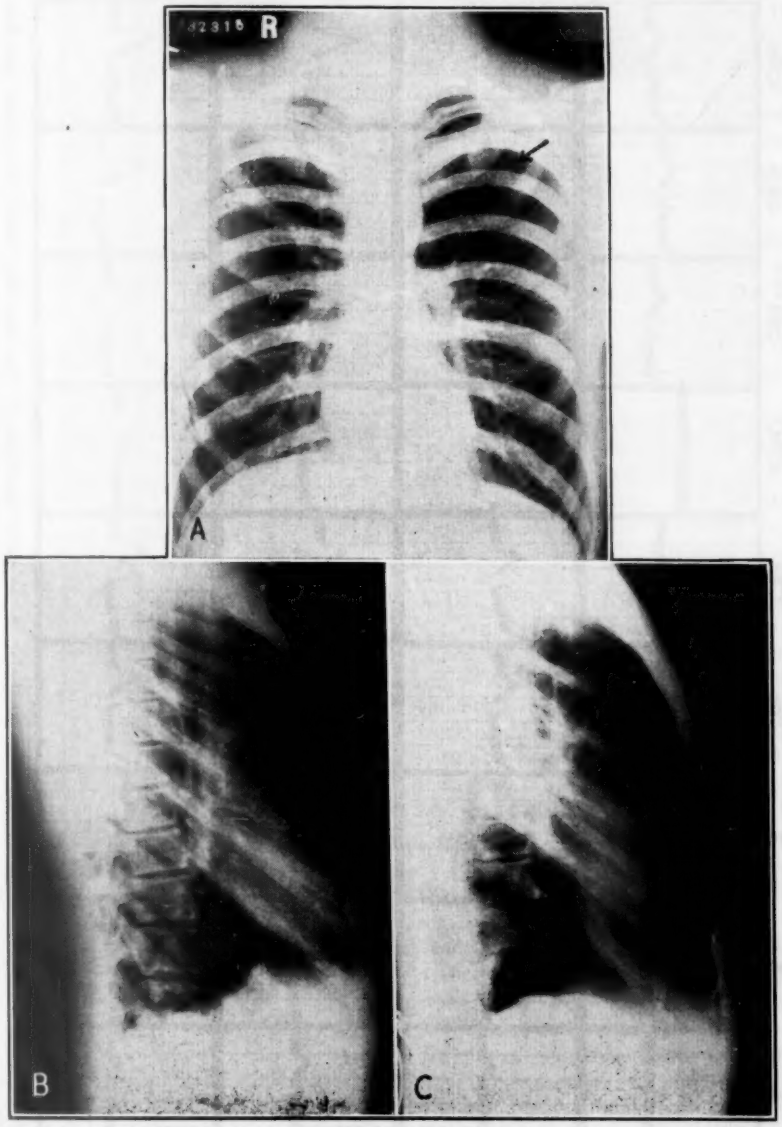

FIG. 1.—Case 1. *A*, Posterior-anterior view of the chest made on the day following admission. Arrow points to the partially collapsed lung. *B*, Left lateral erect view made on the same day. *C*, Left lateral view made in the supine position. Same day.

included the customary limb leads, CF2, 3 and 4, CR2, 3 and 4 in the supine, prone and erect positions, and a continuous tracing of CF3 with the patient on a radiographic tilt table. This tracing was begun with the patient in the supine position. The table was first rapidly erected, then returned to the horizontal plane. After the electrocardiograms were recorded, lateral radiograms were made of the chest with the patient erect and in the supine position.

It was possible to demonstrate by Roentgen ray that there was a great deal more air in the space between the sternum and the heart with the patient in the supine position than when he was erect.

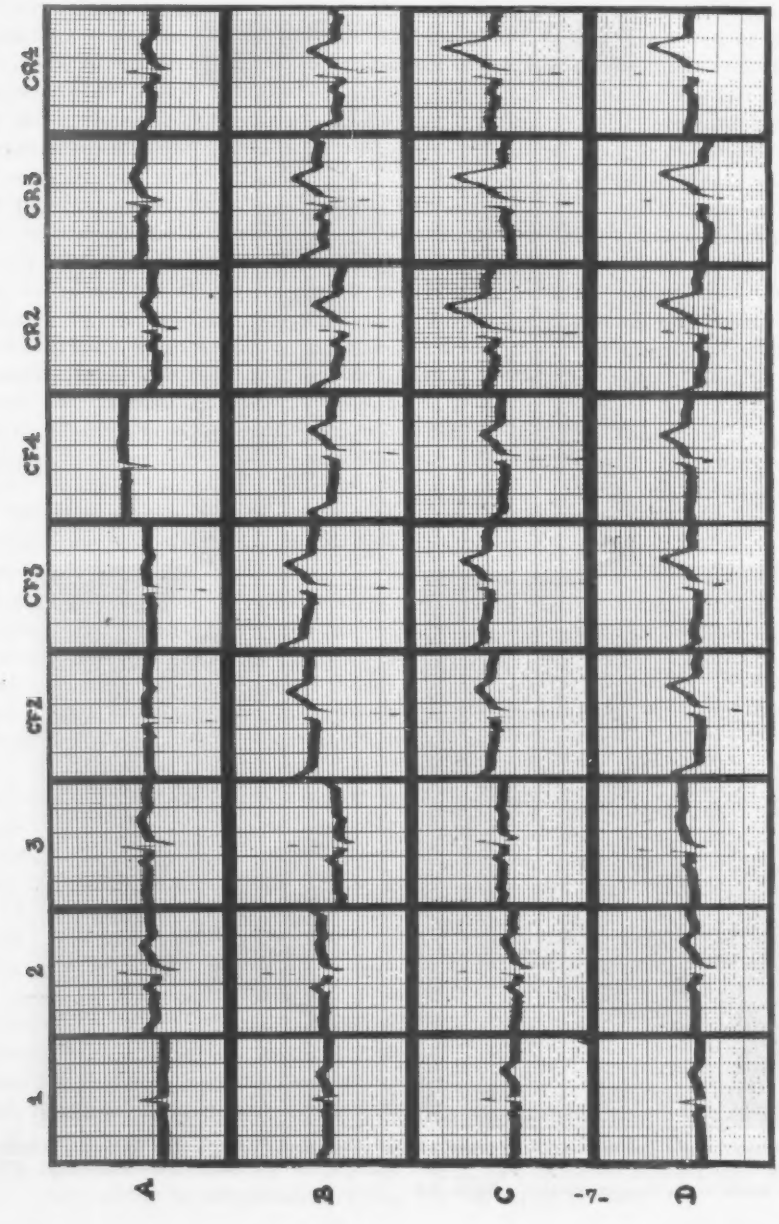

FIG. 2.—Case 1. *A*, Obtained the day after admission in the supine position. *B*, The same day; made in the erect position. *C*, The same day; made in the prone position. *D*, Made upon recovery, in the supine position.

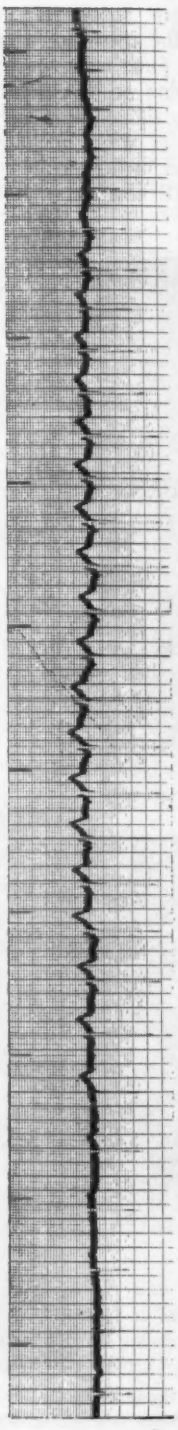

FIG. 3.—Case 1. Lead CF3, recorded on the day after admission. Tracing begun with the patient in the supine position. The table was then rapidly erected and returned to the horizontal position. The central portion of the curve was inscribed when the table was vertical.

The CF leads made with the patient supine showed T waves which were either flat or inverted; the R waves were absent or very small. The CR leads in the same position were essentially normal. T1 was low, T2 and 3 upright and S2 and 3 were prominent. In the erect and prone positions T1 was higher, T2 lower and T3 diphasic to inverted. R1 was higher and S2 and 3 very small. The T waves in the CF leads were erect although the R waves remained small. The T waves in the CR leads were upright and higher and the QRS excursions larger than in the supine position. The continuous tracing made with the patient first supine, then erect and finally supine showed a constantly altering T wave which was first inverted, then erect and finally inverted.

During the period of hospitalization which lasted 15 days the temperature went to 99.4 on several occasions and the WBC to 14,200. Except for moderate precordial discomfort during the first few days noted only in the recumbent position the patient had no complaints.

At the end of this time the mediastinal emphysema and pneumothorax had cleared entirely and the electrocardiogram became normal in all positions. The last curve still showed a rather small R wave in the CF leads but was within normal limits and essentially similar to those tracings made earlier in the erect or prone position.

CASE 2. A 19 year old soldier first experienced substernal pain and oppression approximately 2 weeks before coming into the hospital. This happened while he was working in a tank and was not associated with any severe physical effort. The pain increased in severity to the point where he had to stop his work. However, the pain receded gradually during the succeeding 3 or 4 days and he did not seek medical care. On the afternoon of his entrance into the hospital he was again working on a tank, this time lying under it, when he was taken by a sharp pain under the sternum. The pain was rather more severe than during the first attack and radiated to the left shoulder. He was subsequently admitted to the hospital. The temperature was 97.8°, the pulse 100 and the WBC was 14,300.

The diagnosis was not at once apparent and an electrocardiogram was ordered

together with other laboratory procedures. This demonstrated essentially normal limb leads. However, 4F showed a small initial deflection, elevated ST segment and inverted T wave. He was ordered back to the electrocardiograph laboratory for additional tracings and at this time the physical signs of left-sided pneumothorax with mediastinal emphysema were noted. Roentgen rays were made of the chest and these included PA and lateral films with the patient erect and in the supine position. Electrocardiograms were made, including the customary limb leads and 4F with the patient supine, erect, prone and on his right side, 4R and a continuous 4F tracing with the patient

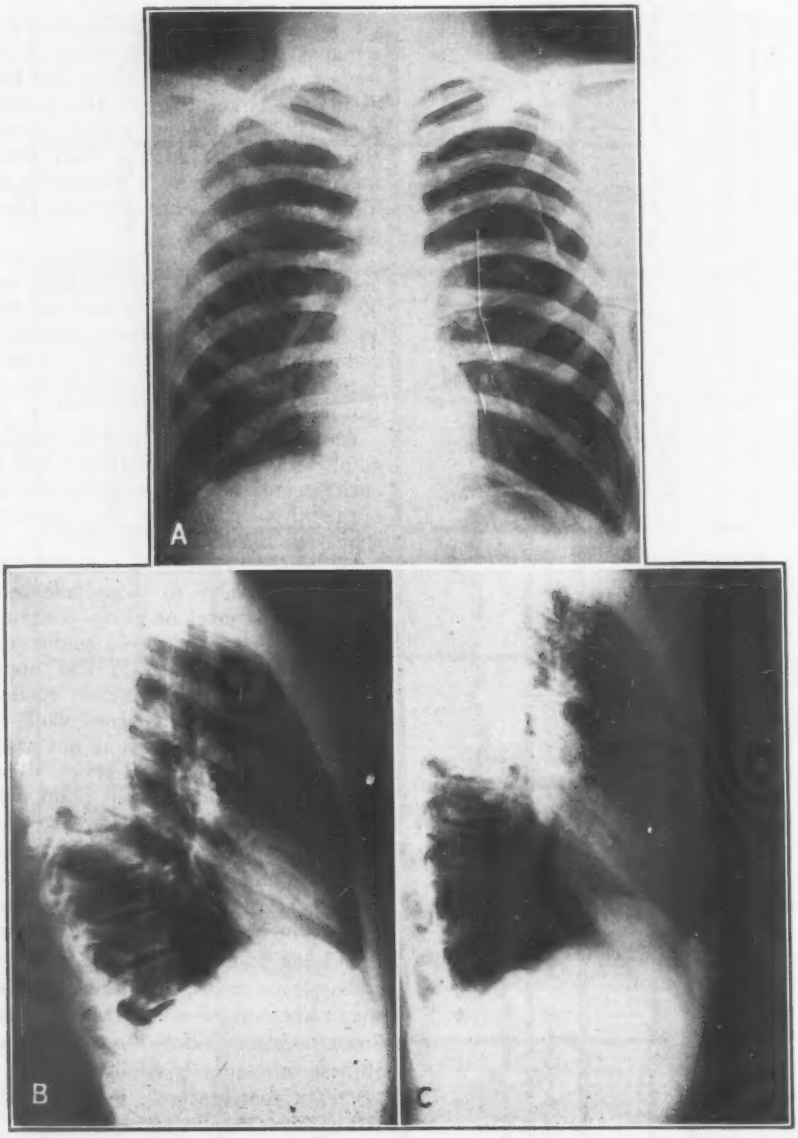

FIG. 4.—Case 2. *A*, A view of the chest made on admission. Pneumothorax clearly indicated. *B*, Left lateral erect view made at the same time. *C*, Left lateral view made in the supine position at the same time.

on a radiographic tilt table as described in Case 1.

The Roentgen rays demonstrated a left-sided pneumothorax with approximately 20% collapse of the lung. A large amount of air was seen in the retrosternal space when the patient was supine and a much smaller quantity when he was erect.

Approximately 1 week after admission the pneumothorax had diminished to approximately one-half of its original extent and the mediastinal emphysema had cleared. At this time the T wave in 4F was erect though low and did not differ materially with the position of the patient. Lead 4R was essentially unaltered.

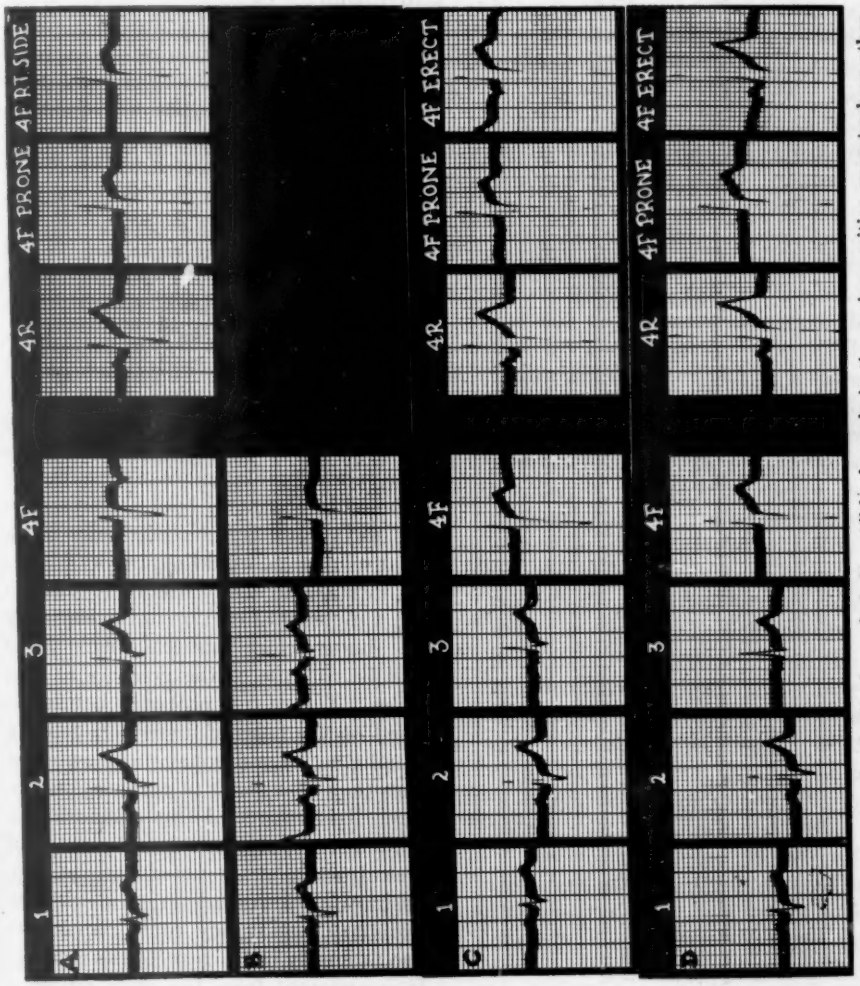

FIG. 5.—Case 2. *A*, Obtained on admission. All leads made in the supine position except where otherwise indicated. *B*, Same day. All leads made in the erect position. *C*, One week later. All supine except as noted. *D*, Upon recovery 3 weeks later. All supine except as noted.

The T wave in 4F was inverted when the patient was supine; it was erect though somewhat low when he was on his right side, prone or erect. The tilting tracing demonstrated continuous alteration of the T wave from inverted to erect to inverted. Lead 4R was entirely normal.

Some 2 weeks later (3 weeks after admission) there was complete clearing of the pneumothorax. An electrocardiogram made at that time was entirely within normal limits. The T wave in 4F was still higher when made in the erect position than in the supine. The tracing did not differ signifi-

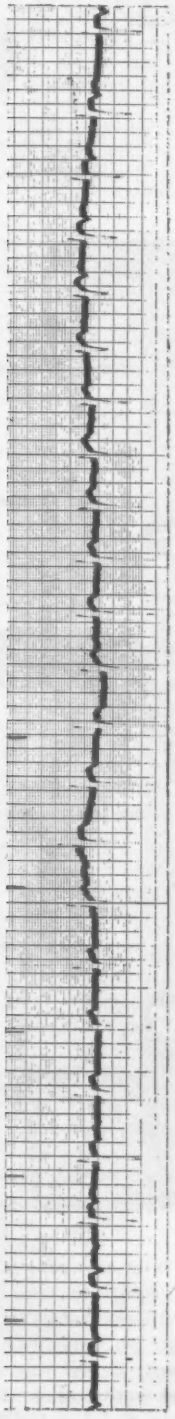

FIG. 6.—Case 2. Lead 4F, obtained on the day of admission. Tracing begun with the patient supine on a radiographic tilt table. The table was then rapidly erected and returned to the horizontal position. The first and last portions of the curve were made when the table was horizontal, the central part when it was vertical

cantly from the one made 2 weeks earlier when some pneumothorax was still present but the mediastinal emphysema had cleared.

Discussion. In this paper we are not concerned with the pathologic physiology of spontaneous mediastinal emphysema with pneumothorax, except where it may help explain the coincidental electrocardiographic phenomena. Macklin[1] has demonstrated that air dissection of the vascular sheaths of the pulmonary vessels may occur and serve to interfere with pulmonary circulation. In support of this conclusion is the case reported by Fisher[2] of a newborn infant who died with mediastinal and interstitial pulmonary emphysema. In this case the right auricle and ventricle were found to be dilated at autopsy. This interference with the pulmonary circulation is logical and understandable. However, it is difficult to see how this phenomenon would serve to impede coronary flow. In mitral stenosis with failure of the left auricle, for example, considerable increase in pulmonary pressure occurs without any interference with coronary circulation. In a similar manner, it would require a tremendous increase in mediastinal pressure to cause significant alteration in the coronary flow. Long before this took place there would be collapse of the great veins and auricles. The pain is probably better explained on the basis of dissection, tearing and splitting of pulmonary and vascular tissues than as a result of coronary inadequacy. In support of this conclusion is the almost instantaneous alteration of the electrocardiogram noted with change of position. Electrocardiographic evidence of coronary inadequacy could hardly occur so promptly or be corrected so rapidly.

It is apparent from the cases reported by Miller and those noted above that extensive electrocardiographic changes may be observed in the presence of mediastinal emphysema and left-sided pneumothorax. It is of further interest that the alterations were largely confined to the precordial lead and that the indifferent electrode

was placed on the left leg. The minor changes observed in the limb leads are not in themselves significant.

From the electrocardiographic data at hand certain observations appear pertinent and significant:

1. Gross electrocardiographic changes in the presence of mediastinal emphysema and left-sided peumothorax are observed only in the CF leads.

2. These changes can be obtained only when the electrocardiogram is made with the patient in the supine position.

3. When the patient is in the prone, erect or right lateral position the tracings are essentially normal.

4. The CR leads are normal in any position although the height of the T waves and size of the QRS excursions show variations.

5. The presence of left-sided pneumothorax without mediastinal emphysema does not produce significant electrocardiographic deviations. (Case 2 at the end of 1 week with clearing of the mediastinal emphysema and persistence of the pneuthorax.)

6. Mediastinal emphysema without left-sided pneumothorax does not produce gross electrocardiographic changes. (Condition which obtains when the pneumothorax is out of the way at the apex of the chest, when patient is erect, or posteriorly when he is prone.)

7. The electrocardiographic changes found with left-sided pneumothorax and mediastinal emphysema in the CF leads when the patient is supine occur instantaneously and can be corrected in a matter of seconds by change of position.

From these observations certain conclusions are probable. It is apparently necessary to have both mediastinal emphysema and left-sided pneumothorax to produce the electrocardiographic deviations described above. Additionally, the pneumothorax must be present in front of the heart. Finally the changes are observed to a significant degree only in the CF leads. It is likely, therefore, that the observed variations are not the result of diminution in the coronary flow but of interference with the normal distribution of the electrical impulse on the surface of the chest.

Katz and his associates[5,6,12] have postulated that the configuration of the electrocardiogram is dependent to a large extent on the character of the tissues interposed between the heart and the electrodes. In a series of experiments during which they inserted rubber dams between the heart and its contiguous structures they were able to demonstrate marked variations in electrical potential dependent upon the position of the insulator. Stated another way, if the currents generated in the living heart produce a given curve when obtained from 2 electrodes on the surface of the body, this curve will alter if these currents are forced to complete their circuit by a different pathway. The electrodes will then be in either a more or less favorable position and the tracing will reflect this difference. In the cases under discussion this occurs when a non-conductor, air, is interposed between the myocardium and the exploring electrode. A somewhat similar explanation[12] is offered for the difference observed in the precordial electrocardiogram of young children as compared with adults. Since normally the largest portion of the electrical current of the heart is conducted away by the posterior muscle masses and the great vessels,[6] little change is expected or found in the limb leads in the presence of mediastinal emphysema with pneumothorax. On the other hand, that portion of the current conducted to the front of the chest is seriously interfered with by the presence of air and results in the gross changes described. One must postulate further that the potentials existing between the right arm and the precordium are not interfered with to the same extent as those between the heart and the left leg. That some interference exists is indicated by the diminution in the height of the T wave in the CR leads when the patients were supine.

It is possible that if the mediastinal

emphysema were of sufficient magnitude the extensive electrocardiographic changes would be found without the simultaneous presence of left-sided pneumothorax. In the cases described, however, it is apparent that the additional insulation afforded by the pneumothorax when the air is in front of the heart is necessary to produce the alterations described. On the other hand, the pneumothorax alone cannot obliterate the precordial conduction tissue sufficiently to cause significant changes.

To reiterate, the cardiac action currents reach the chest wall largely *via* the connective tissue which lies between the heart and the sternum and by direct contact of the pericardium to the chest wall. When the connective tissue becomes infiltrated with air its conductivity becomes impaired and corresponds to that of lung tissue which normally is minimal.[6] However, conduction continues to take place where the heart is in contact with the chest wall to the left of the sternum. When this, too, is obliterated by the presence of a shifting pneumothorax in the supine position, the circuit is completed by a totally different route and results in gross alterations of the electrocardiogram. If the pneumothorax is sufficient in degree with extensive collapse of the lung the shifting phenomenon would probably not take place.

In view of the fact that the only gross abnormalities were noted in the CF leads obtained in the supine position, it would appear logical to employ other leads and positions when electrocardiographic variants are encountered.

Summary. 1. Two cases of mediastinal emphysema with spontaneous left-sided pneumothorax are described, together with the electrocardiographic changes encountered.

2. Evidence is submitted in support of the hypothesis that the electrocardiographic alterations observed are the result of the presence of air between the heart and the exploring electrode, causing interference with electrical conduction; and that the changes are not the result of impedence of the coronary circulation.

3. It is recommended that CF leads be made in various positions and that CR leads be taken.

One additional instance of left-sided spontaneous pneumothorax with mediastinal emphysema was observed since this paper was submitted. This occurred in a young man who was being studied for the late results of trench foot. The incident took place in the hospital and was not associated with physical effort. The same characteristic electrocardiographic changes were noted in the CF leads made in the supine position. Nine days later, coincident with clearing of the physical and radiographic findings, the electrocardiogram became entirely normal.

REFERENCES

1. Bourne, G.: Brit. Med. J., **2**, 313, 1940.
2. Burton, S. D., and Mehlman, J. S.: J. Lab. and Clin. Med., **27**, 465, 1942.
3. Fisher, J. H.: Canad. Med. J., **44**, 27, 1941.
4. Hamman, L.: Ann. Int. Med., **8**, 417, 1934; Trans. Assn. Am. Phys., **52**, 311, 1937; Bull. Johns Hopkins Hosp., **64**, 1, 1939.
5. Katz, L. N., and Korey, H.: Am. J. Physiol., **111**, 83, 1935.
6. Lindner, E., and Katz, L. N.: Am. J. Physiol., **125**, 625, 1939.
7. Macklin, C. C.: Canad. Med. Assn. J., **36**, 414, 1937; Arch. Int. Med., **64**, 913, 1939.
8. Master, A. M.: Am. Heart J., **3**, 472, 1928.
9. Master, A. M., Dack, S., Kalter, H. H., and Jaffe, H. L.: Am. Heart J., **14**, 297, 1937.
10. Master, A. M., Kalter, H. H., and Dack, S.: J. Mt. Sinai Hosp., **8**, 89, 1941.
11. Miller, H.: Am. J. Med. Sci., **209**, 211, 1945.
12. Robinow, M., Katz, L. N., and Bohning, A.: Am. Heart J., **12**, 88, 1936.
13. Scott, A. M.: Lancet, **1**, 1327, 1937.
14. Weinstein, J.: Med. Rec., **153**, 18, 1941.

SOME FACTORS THAT MODIFY THE EFFECT OF TRISODIUM CITRATE ON THE ABSORPTION OF ORAL PENICILLIN

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Since the demonstration by Free, Leonards, McCullagh and Biro[6] that appreciable quantities of penicillin may be absorbed from the normal gastro-intestinal tract, numerous subsequent reports have confirmed the fact that the oral administration of penicillin may produce therapeutically effective blood levels. All such reports have agreed to the extent that relatively large doses of oral penicillin are necessary for the establishment of such blood levels. From the viewpoint of the quantities required, the oral administration of penicillin must therefore be considered an inefficient method of therapy as compared to parenteral injection. However, in view of the obvious advantages inherent to oral therapy, efforts have been devoted to devise means for increasing the absorption of oral penicillin. Accordingly, numerous studies have been made on the effect of various adjuvants and vehicles on the absorption of oral penicillin.

Of the many adjuvants proposed for use with oral penicillin, gastric antacids have received much attention and a number of investigators have recorded the beneficial effect of the addition of various alkalies to penicillin, whereas other reports have failed to demonstrate any marked advantage in their use. György *et al.*,[7] working largely with children and infants, concluded that the simultaneous administration of trisodium citrate led to more prolonged and higher blood levels than when penicillin was administered alone. Charney, Alburn and Bernhart[3] substantially confirmed the conclusions of György and his collaborators, but noted a somewhat lesser effect. Cutting, Halpern, Sultan, Armstrong and Collins[4] have also demonstrated the beneficial effect of alkalies. Other reports have noted a similar effect of aluminum hydroxide.[13] On the other hand, such reports as those by McDermott *et al.*[10] and Finland, Meads and Ory[5] failed to demonstrate that the addition of alkalies markedly affected the extent of absorption. Numerous other uncited reports have confirmed one or the other of the two groups of investigators. Thus, although many reports have been published concerning the oral administration of penicillin, various claims remain unconfirmed and there still exists a marked disagreement concerning the effect of antacids.

Unfortunately, it has not been possible to establish a valid basis for the comparison of such results as those cited above inasmuch as the administration of oral penicillin has not always been investigated under comparable conditions. Thus, whereas György *et al.*[7] determined absorption in infants and children, others[4,5,10] worked principally with adults. The size of the individual doses administered has also varied from 20,000[3,7] to 315,000[10] units. Certain groups[4,7,10] have reported the extent of absorption primarily in fasting subjects, others[3,5] have investigated in detail absorption in both the fasting and the post-absorptive state. Finland, Meads and Ory[5] reported results obtained from the use of some proprietary preparations, the nature of which has been kept a secret.

In a preliminary communication,[11] we investigated some of the factors that appeared to influence the absorption of

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oral penicillin by normal adults. Our results indicated that both the size of the dose and its relation to mealtime may have an important influence on the effect of trisodium citrate on the absorption of oral penicillin. These results are reported here in the hope that they may be useful in reconciling some of the inconsistencies noted in previous investigations.

Methods. Young, healthy, adult, male volunteers were given different dosages of penicillin either before or after mealtime, usually breakfast, and blood levels and, in many instances, total urinary excretions were determined at intervals subsequent to its administration. Calcium penicillin plus trisodium citrate was given in the form of tablets, each tablet containing 1 gm. of citrate plus 25,000 units of calcium penicillin. Calcium penicillin "without buffer" was administered in ordinary gelatin capsules, each capsule containing 50,000 units intimately mixed with lactose as a filler.

Penicillin was determined in both serum and urine by a slight modification of the serial-dilution method of Hobby, Meyer and Chaffee.[6] All determinations were made in conjunction with duplicate standards of calcium penicillin with the C203MV strain of hemolytic streptococcus as the test organism. In the conditions used, this organism was sensitive to approximately 0.01 units per ml. when the presence or absence of grossly visible growth after 24 hour incubation was used as the sole indicator.

Following ingestion of the penicillin, all subjects were permitted to perform their ordinary duties during the intervals between assays and were not cautioned in regard to restriction of fluids.

Results. Since our original report, our experience has been increased to include the results of blood and urine assays performed on over 150 subjects. One subject who ingested 175,000 units of penicillin plus 7 gm. of trisodium citrate on a fasting stomach became temporarily nauseated. None of the other subjects complained of any ill-effects from any of the preparations used.

For the sake of clarity the results are summarized under a number of different headings. In deference to brevity, representative results are presented rather than a detailed list of all assays performed.

1. Calcium Penicillin ("Without Antacid"). (*a*) *One Hour After Breakfast.* The results in Table 1 demonstrate that the administration of 100,000 units 1 hour before breakfast generally resulted in appreciable blood levels for 2 hours and in the recovery of appreciable but variable amounts in the urine over a 12 hour period. The ingestion of 50,000 units resulted in appreciable but usually markedly decreased urinary excretions. Less than 0.0125 units per ml. were generally present in the serum. Our failure to produce satisfactory blood levels by administration of 50,000 units was somewhat disappointing but not entirely unexpected since others[4] have also noted that "It is probable that there would be many failures with single doses of 50,000 units of penicillin."

(*b*) *One Hour After Breakfast.* The results in Table 2 illustrate the fact that the administration of either 50,000 or 100,000 units usually resulted in negative blood levels and relatively insignificant urinary excretions.

2. Calcium Penicillin With Trisodium Citrate. (*a*) *One Hour Before Breakfast.* The results in Table 3 illustrate the satisfactory blood levels that were found for 2 to 3 hours after the administration of either 50,000 or 100,000 units. The same results indicate high percentages of urinary recovery but subjects with similar blood levels frequently were found to excrete markedly divergent amounts of penicillin.

(*b*) *One Hour After Breakfast.* The results of Table 4 indicate that, in general, both the blood levels and the urinary excretions were similar to those obtained when penicillin was administered to the fasting subject.

Discussion. The importance of the size of the individual dose as a determinant of the effect of trisodium citrate on the absorption of oral penicillin does not appear to have received adequate emphasis. In general, the blood concentrations obtained after administrations of various quantities

of penicillin increase with the size of the dose. However, this increase is not directly proportional to the dose, successive increases of the latter producing decreasing increments in the height of the blood level.[4]

If trisodium citrate protects penicillin against destruction by the gastric acid, the administration of a given dose of penicillin with trisodium citrate would, in effect, be equivalent to administration of a somewhat larger dose of penicillin alone.

TABLE 1.—ORAL ADMINISTRATION OF CALCIUM PENICILLIN, 1 HOUR BEFORE BREAKFAST

Dosage (units)	Serum levels in units penicillin per ml. Hours after administration 1	2	3	4	Total units penicillin recovered in urine over 12 hours
100,000	0.2	0.025	0	0	26,524
100,000	0.2	0.025	0	0	23,494
100,000	0.2	0.05	0	0	42,953
100,000	0.1	0.025	0	0	6,984
100,000	0.2	0.0125	0	0	5,881
100,000	0.1	0.05	0.025	0	*
50,000	0.025	0	0	0	6,573
50,000	0	0	0	0	1,290
50,000	0.025	0	0	0	13,832
50,000	0.025	0.025	0	0	14,772
50,000	0	0	0	0	2,088
50,000	0	0	0	0	*

* Not estimated.

TABLE 2.—ORAL ADMINISTRATION OF CALCIUM PENICILLIN 1 HOUR AFTER BREAKFAST

Dosage (units)	Serum levels in units penicillin per ml. Hours after administration 1	2	3	4	Total units penicillin recovered in urine over 12 hours
100,000	0	0	0	0	2753
100,000	0	0	0	0	1597
100,000	0	0	0	0	1983
100,000	0	0.0125	0	0	1134
100,000	0	0	0	0	*
100,000	0	0	0	0	*
50,000	0	0	0	0	865
50,000	0	0	0	0	1019
50,000	0	0	0	0	*
50,000	0.0125	0	0	0	*
50,000	0.0125	0.0125	0	0	*

* Not estimated.

TABLE 3.—ORAL ADMINISTRATION OF CALCIUM PENICILLIN WITH TRISODIUM CITRATE 1 HOUR BEFORE BREAKFAST

Dosage (units)	Serum levels in units penicillin per ml. Hours after administration 1	2	3	4	Total units penicillin recovered in urine over 12 hours
100,000	0.4	0.05	0.025	0.0125	23,680
100,000	0.2	0.1	0.05	0.0125	42,748
100,000	0.2	0.025	0	0	5,309
100,000	0.4	0.1	0	0	30,076
100,000	0.4	0.05	0.025	0	41,502
50,000	0.05	0.05	0	0	16,949
50,000	0.2	0.1	0.0125	0	13,628
50,000	0.1	0.025	0	0	8,797
50,000	0.2	0.025	0	0	*
50,000	0.1	0.05	0	0	*

* Not estimated.

It would follow that the effect of trisodium citrate should be most marked when given with smaller doses of penicillin. Actually, such seems to be the case. A marked effect of trisodium citrate on the absorption of 20,000 to 40,000 units has been described.[3,7] Our results and those of others[4] demonstrate a similar action with 50,000 units. The results in Tables 1 and 3 and those of Finland, Meads and Ory[5] show little, if any, effect after 90,000 to 100,000 units and no effect has been found with still larger doses.[10] It is therefore attractive to postulate that many of the apparent inconsistencies cited above in regard to the effect of the simultaneous administration of penicillin with trisodium citrate disappear when due consideration is given to the size of the dose.

TABLE 4.—ORAL ADMINISTRATION OF CALCIUM PENICILLIN WITH TRISODIUM CITRATE 1 HOUR AFTER BREAKFAST

Dosage (units)	Serum levels in units penicillin per ml. Hours after administration 1	2	3	4	Total units penicillin recovered in urine over 12 hours
100,000	0.4	0.1	0.025	0.025	37,000
100,000	0.8	0.1	0	0	36,000
100,000	0.2	0.1	0.0125	0	29,400
100,000	0.025	0.025	0	0	14,514
50,000	0.1	0.1	0.05	0	15,592
50,000	0.1	0.1	0	0	17,800
50,000	0.4	0.05	0	0	26,000
50,000	0.025	0	0	0	3,226

The original demonstration by Rammelkamp and Helm[12] that penicillin was readily absorbed from the gastro-intestinal tract of achlorhydric patients has been repeatedly confirmed.[4,5] Accordingly, there is a theoretical justification for the inclusion of an antacid in preparations of oral penicillin. However, if trisodium citrate is effective by virtue of its tendency to protect penicillin from destruction by the gastric juice, it should be most effective under conditions in which there is a maximum interference with the absorption of penicillin as a result of the increased production of acid. Inasmuch as gastric secretion is stimulated by the ingestion of food, minimal absorption of penicillin might be anticipated to occur in the postprandial state. György *et al.*[7] demonstrated that such was the case and their observations have been confirmed by others[3,5] and by the results in Tables 1 and 2. Furthermore, the charts of Finland, Meads and Ory[5] demonstrate that in patients with pernicious anemia, in whom the ingestion of food fails to stimulate acid production, there is less interference in the absorption of penicillin after mealtime than in normal subjects.

We believe that this effect of the previous ingestion of food is, in fact, in part due to the destruction of a large proportion of the penicillin so that, in reality, the quantity of effective penicillin available for absorption represents but a small fraction of the quantity actually given. In other words, the administration of 100,000 units after mealtime is presumed equivalent to the administration of, say, 30,000 units to a fasting subject. If, however, the addition of trisodium citrate could prevent the destruction of such a large proportion of the penicillin, the postprandial administration of 100,000 units with trisodium citrate might be expected to give results similar to those obtained after ingestion of approximately the same quantity by a fasting subject. Charney, Alburn and Bernhart[3] first demonstrated this decidedly beneficial effect of trisodium citrate after meal time. Our results in Tables 1, 2, 3 and 4 are in complete agreement and indicate that the theoretical deductions concerning the effect of trisodium citrate on the postprandial absorption of penicillin conform to the experimental observations. We are at a loss to

explain the findings of Finland, Meads and Ory[5] who concluded that no beneficial effect was obtained by the use of "buffers." However, even in their experience, aluminum hydroxide gel gave somewhat better results after mealtime.

Just as is the case in the administration of penicillin to the fasting subject, we anticipate that the effect of trisodium citrate will become decreasingly evident as the size of the postprandial dose is progressively increased. Indeed, a few trials with 500,000 units have given evidence of such a decreasing effect but such experiments have been too few to warrant definite conclusions.

However, we have been unable to demonstrate that the oral administration of penicillin markedly prolongs the maintenance of effective blood levels. Indeed, analysis of the rates of excretion in Table 5 indicates that although the antacid may influence the total quantity of penicillin absorbed, such a quantity is rapidly excreted from the body. These conclusions are supported by the figures for the blood assays, since, in general, blood levels tended to fall below therapeutically effective values in 3 hours or less.

These results indicate the necessity for the frequent repetition of oral doses for the maintenance of effective blood levels

TABLE 5.—RATES OF EXCRETION OF PENICILLIN ADMINISTERED BY MOUTH

Dosage (units)	Total units penicillin excreted in urine over 12 hours	% penicillin (cumulative) of total excreted in urine over 12 hours				
		Hours after administration				
		2	4	6	8	10
With citrate						
1 hour before meal						
100,000	9,005	42.6	93.8	98.0	99.3	99.9
100,000	43,198	59.0	94.6	98.7	99.8	100.0
50,000	8,797	51.7	94.6	99.6	99.8	100.0
50,000	16,949	93.6	97.0	99.1	99.6	100.0
1 hour after meal						
100,000	14,514	57.3	94.8	97.9	99.5	100.0
100,000	29,400	65.3	95.8	98.8	99.7	100.0
50,000	3,226	71.4	87.8	97.6	99.5	100.0
50,000	27,930	50.0	81.2	97.0	99.7	100.0
Without citrate						
1 hour before meal						
100,000	6,984	69.6	93.0	98.7	99.7	100.0
100,000	42,953	85.8	94.7	99.5	99.9	100.0
50,000	1,290	90.5	99.9	100.0	100.0	100.0
50,000	6,573	82.8	99.8	100.0	100.0	100.0
1 hour after meal						
100,000	1,134	70.5	85.3	96.9	100.0	100.0
100,000	2,753	87.2	98.0	99.8	100.0	100.0
50,000	486	62.2	96.9	99.9	100.0	100.0
50,000	1,019	68.7	88.7	98.3	99.9	100.0

The arguments and facts presented above should not be interpreted as a proof of any decided advantage of trisodium citrate over other antacids for we believe that any effective non-toxic antacid will produce similar effects. Cutting *et al.*[4] noted no marked differences between the activities of 3 such alkalies and other reports have established the advantages of various other antacids.[9,12]

just as in the case of parenteral therapy. Such a consideration emphasizes anew the advantage of the use of an antacid since oral penicillin therapy should conceivably be continued throughout the day without interference by meals. The principal present objection to the widespread use of oral penicillin therapy resides in the greater quantities required for successful treatment. The results of Györgi *et al.*[7]

and Charney, Alburn and Bernhart,[3] as well as those in this report, indicate that smaller quantities of penicillin may be required to overcome the interference of eating if used in conjunction with an antacid. Thus, frequent repeated doses may be given safely without regard to mealtime. There is little doubt that larger doses may be effective without an alkali and Bunn, McDermott, Hadley and Carter[2] have reported on the successful treatment of pneumonia by the oral administration of penicillin without an added antacid. However, they felt constrained to employ 5 times as large a dosage as that required for intramuscular therapy. In contrast, we have reported[1] the successful treatment of gonorrhea by oral penicillin plus trisodium citrate and have used only 2½ times the total dosage required by the Army for treatment by intramuscular therapy. Obviously, any factors which tend to decrease the differential between the total dosages of penicillin required for intramuscular and oral therapy would tend to operate in favor of adoption of the latter as the method of choice.

Summary and Conclusions. 1. The influence of the size of the dose, its relation to meal time and the effect of trisodium citrate on the absorption of oral penicillin were investigated in a series of normal adult subjects.

2. Appreciable absorption of calcium penicillin occurred in fasting subjects given a dose of 100,000 units but not with a dose of 50,000 units. Neither dose resulted in appreciable absorption when given 1 hour after breakfast.

3. In fasting subjects, the addition of trisodium citrate to calcium penicillin markedly increased the absorption of 50,000 units but the effect on the absorption of 100,000 units was less pronounced. In subjects given calcium penicillin 1 hour after breakfast, the addition of trisodium citrate markedly increased the absorption of both 50,000 and 100,000 units.

4. Although the various factors influenced the total quantity of penicillin absorbed, they did not appear to affect the rate of its excretion from the body.

5. Statements concerning the effect of antacids on the absorption of oral penicillin should be qualified by consideration of the dose and its relation to eating. It is concluded that the effect of trisodium citrate and of eating becomes less pronounced with progressive increase in the size of the dose and that the maximum advantage of the inclusion of trisodium citrate in a dose of oral penicillin is observed after administration of smaller doses.

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REFERENCES

1. Broh-Kahn, R. H., AAFSAM Research Project Report, No. 404, AAF School of Aviation Medicine, 1945.
2. Bunn, P. A., McDermott, W., Hadley, S. J., and Carter, A. C.: J. Am. Med. Assn., **129**, 320, 1945.
3. Charney, J., Alburn, H. E., and Bernhart, F. W.: Science, **101**, 251, 1945.
4. Cutting, W. C., Halpern, R. M., Sultan, E. H., Armstrong, C. D., and Collins, C. L.: J. Am. Med. Assn., **129**, 425, 1945.
5. Finland, M., Meads, M., and Ory, E. M.: J. Am. Med. Assn., **129**, 315, 1945.
6. Free, A. H., Leonards, J. R., McCullagh, D. R., and Biro, B. E., Science, **100**, 431, 1944.
7. György, P., Vandergrift, H. N., Elias, W., Colio, L. G., Barry, F. M., and Pilcher, J. D.: J. Am. Med. Assn., **127**, 639, 1945.
8. Hobby, G. L., Meyer, K., and Chaffee, E.: Proc. Soc. Exp. Biol. and Med., **50**, 277, 1942.
9. Krantz, J. C., Evans, W. E., and McAlpine, J. G.: Science, **101**, 618, 1945.
10. McDermott, W., Bunn, P. A., Benoit, M., DuBois, R., and Haynes, W.: Science, **101**, 228, 1945.
11. Pedrick, R. F., and Broh-Kahn, R. H.: AAFSAM Research Project Report No. 388, AAF School of Aviation Medicine, 1945.
12. Rammelkamp, C. H., and Helm, J. D., Jr.: Proc. Soc. Exp. Biol. and Med., **54**, 324, 1943.
13. Welch, H., Price, C. W., and Chandler, V. L.: J. Am. Med. Assn., **128**, 845, 1945.

EFFECT OF ANTIMONY ON THE ELECTROCARDIOGRAM

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TRIVALENT and pentavalent antimony compounds have been used extensively in the treatment of human schistosomiasis and leishmaniasis and more recently to a limited degree in human filariasis. The major application of antimony as a therapeutic agent in the recent war has been its use in the treatment of schistosomiasis japonica. Fuadin and tartar emetic, both trivalent antimonials, are the drugs principally used in the treatment of this infection. Pentavalent antimony compounds (neostam, neostibosan and stibanose) have had only limited application during the war to a relatively small number of cases of leishmaniasis and to a less degree in the experimental treatment of filariasis. It is anticipated that a number of individuals with schistosomiasis will require retreatment subsequent to their release from military service and such treatment will be given in private practice or at veteran facilities. It is therefore our purpose in this paper to report certain changes in the electrocardiogram which have been observed during treatment of schistosomiasis patients at this hospital with tartar emetic and fuadin.

In 1939 Mainzer and Krause,[5] in attempting to explain sudden deaths which occur during antimony therapy, made a study of electrocardiographic changes in 12 schistosomiasis patients during treatment with tartar emetic. They found ST-interval and T-wave changes which were "definitely pathological" in 3 cases, suspicious in 4 cases, and insignificant in 2 cases. They believed these changes to be due to the direct effect of antimony on the myocardium, and explained cases of sudden death on the bases of an exaggeration of this same toxic action resulting ultimately in auricular (?) fibrillation and death. Tarr[7] recently reported T-wave changes in approximately 80% of 66 patients during treatment with antimony for infections with *Schistosoma japonicum*. These changes, consisting in lowering or inversion of T waves in all leads, occurred in 100% of the patients receiving tartar emetic and in 53% of those receiving fuadin.

This paper concerns itself with an analysis of electrocardiograms taken on 100 patients during treatment with tartar emetic and fuadin. These patients were all observed and treated at Moore General Hospital, between April and December 1945 for infections with *S. japonicum* and *S. mansoni*. In none of these cases was there any clinical evidence of cardiovascular disease either before, during or after therapy, nor did any fatality occur.

Methods. Patients in this study were treated with either fuadin (a trivalent antimony compound given intramuscularly in 6.4% solution) or tartar emetic (also a trivalent antimony compound given intravenously in freshly prepared 0.5% solution in 10% glucose). The following treatment schedules were used:

1. *Fuadin 70 cc.* The entire course of treatment lasted 27 days. Patients received 1.5, 3.5 and 5 cc. on Days 1, 2 and 3, respectively. Then 5 cc. were given intramuscularly every other day for 12 injections until a total of 70 cc. had been given. Total amount of fuadin was 4.48 gm., representing 0.599 gm. of antimony.

2. *Fuadin 100 cc.* The entire course of treatment lasted 14 days, 2, 4 and 6 cc. being given on Days 1, 2 and 3, respectively, and then 8 cc. intramuscularly every day

for 11 injections until a total of 100 cc. had been given. Total amount of fuadin was 6.4 gm., representing 0.870 gm. of antimony.

3. *Tar Emetic 1.45 gm.* The entire course of treatment lasted 31 days, 5, 10 and 15 cc. of 0.5 solution being given on Days 1, 3 and 5, and then 20 cc. intravenously every other day for 13 injections, until a total of 290 cc. had been given. Total amount of tartar emetic was 1.45 gm., representing 0.522 gm. of antimony.

4. *Tartar Emetic 1.8 gm.* The entire course of treatment lasted 29 days, with 8, 12, 16, 20 and 24 cc. of 0.5% solution given on Days 1, 3, 5, 7 and 9, respectively, and then 28 cc. intravenously every other day for 10 injections, until a total of 360 cc. had been given. Total amount of tartar emetic was 1.8 gm., representing 0.648 gm. of antimony.

Electrocardiograms were taken before and at various times during and after treatment. This study is based on a total of 315 such records taken on 100 patients who had received one of the above courses of antimony therapy as treatment for schistosomiasis. Some of the patients had only 2 cardiograms taken, *i. e.*, a control and a record taken during or immediately after antimony therapy while others had more frequent observations. Unfortunately, in many cases the maximum effect of therapy was not recorded because electrocardiograms either were taken too early in the course of treatment or, in some cases, were taken several days after the completion of antimony.

All records were taken with the patient in the supine position. The standard limb leads and CF_4 were used. Records were carefully standardized so that 1 mv. caused a deflection of 10 mm. When actual measurement revealed this distance to be less than 9 or more than 11 mm. the record was excluded from this study. In this paper electrocardiographic changes will be described in the accepted terms for various electrical components and time intervals as advocated in "Nomenclature and Criteria for Diagnosis of Diseases of the Heart."[6]

Results. *The Heart Rate.* No changes were observed in the heart rates of patients during antimony therapy. The mean heart rate in the 100 control records was 78.2 per minute as compared to 78.7 per minute during treatment.

P Waves. Many of our patients showed the commonly seen variations in amplitude and contour of P_3, usually with the respiratory cycle. These changes, being within normal limits, were disregarded. However, in 11% of the patients a definite increase in the amplitude of P waves in Leads 2 and 3 occurred during antimony therapy. In addition, the contour of P_2 and P_3 was altered from smooth rounded curves to tall, sharp, peaked waves. In some cases the increase in amplitude in Lead 3 resulted in an inverted or diphasic P wave becoming tall, upright and peaked. No change was noted in the actual duration in time of the P deflection. Records illustrating these changes are shown in Figures 1, 2 and 3.

Of the 11 cases showing these P-wave changes, 9 showed alteration of both P_2 and P_3, while in the remaining patients Lead 2 alone was involved. No significant changes were noted in P waves in Leads 1 and 4. Generally speaking, records showing the most marked alterations in P waves also showed considerable change in T waves which will be described later. However, numerous records showing pronounced effect of antimony on T waves showed no change in P waves from control levels.

The duration of this abnormality is difficult to determine in this study because of an insufficient number of records taken after completion of therapy. However, records on 1 patient show the P waves to be still altered 15 days after therapy and to have returned to control levels 40 days after treatment. In other cases showing P-wave changes during antimony treatment, records taken 40, 50 and 60 days after therapy revealed P waves identical with those in control records. In still another patient P_2 and P_3 had shown little tendency to return to control levels 56 days after the last injection. From these rather spotty observations no definite conclusions as to duration of P-wave changes after cessation of therapy can be drawn. However, it is apparent that in some patients these changes may

persist for as long as 2 months after completion of therapy with antimony.

PR Interval. No change in PR interval was found during antimony therapy. The mean PR interval before therapy was 0.148 second as compared to 0.1492 second during treatment.

QRS Complex. The antimony therapy caused no change in contour or amplitude of QRS complexes. In all cases the duration of QRS was within normal limits both before and during antimony therapy. No changes in electrical axis were noted.

ST Segment. In 7% of our patients it was noted that slight elevation or depression of the ST segments, not previously observed in the control records, occurred during antimony therapy. In all cases these changes were very slight in degree, approximating 1 mm., and followed no specific pattern as to which leads were involved. ST_1 and ST_2 were elevated on

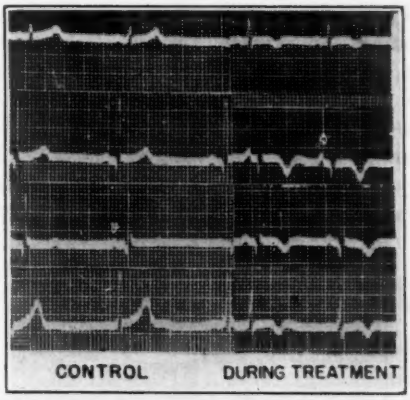

FIG. 1.—Electrocardiographic changes during administration of tartar emetic. "Control" record before treatment. "During Treatment" record taken on the 32nd day of therapy 24 hours after injection of 20 cc. of 0.5% solution. Total dose prior to this record was 290 cc. of 0.5% solution tartar emetic = 1.45 gm. = 0.522 gm. antimony. Note increase in height in P_2 and P_3 and inversion of all T waves. QT interval prolonged. Record taken 50 days after completion of treatment showed disappearance of abnormalities noted during treatment.

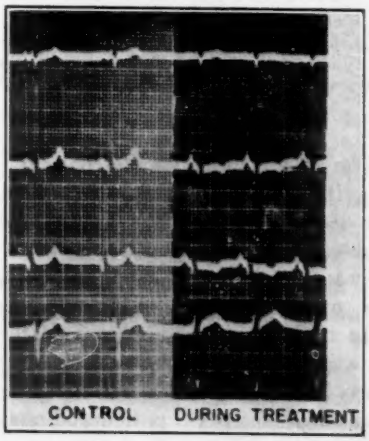

FIG. 2.—Electrocardiographic changes during administration of tartar emetic. "Control" record prior to treatment. "During Treatment" record taken 48 hours after last dose of 20 cc. of 0.5% solution tartar emetic. Total course of treatment consisted of 1.45 gm. (see text for schedule of administration). Note increase in P_2 and P_3 and decreased amplitude of T wave in Lead 1 and inversion of Leads 2 and 3.

2 records, depressed in none; ST_3 was never elevated but was depressed in 2 records; and ST_4 was elevated on 5 occasions and never depressed.

A more common change involving the ST segment and occurring in 45% of the patients during antimony therapy consisted of fusion of the ST segment with the T wave so that the 2 were very difficult to separate. In many normal electrocardiograms it is impossible to find a definite point where the ST segment ends and the T wave begins, so that the determination of which records in this study showed ST–T fusion was by necessity on an arbitrary basis. In normal records the most frequently occurring contour of the ST segment is a concavity upwards so that, as ST merges into an upright T wave, a change in direction of the curve to an upward convexity takes place.[4] In many of our records the ST segment was convex at its origin and merged into a somewhat lowered T wave to form a single convex curve which could not be separated into ST segment and T wave components. To some extent this change is the natural result of decreasing the amplitude of the T wave but in many records there appears to be an actual change in the ST segment, as well, producing a single smooth curve.

In some cases this abnormality was transient in nature, occurring fairly early in treatment and disappearing later in the course of antimony therapy when T-wave changes became more marked. The relative frequency of occurrence of ST–T fusion in different leads was as follows: Lead 1, 55.6%; Leads 2 and 4, 53.4%; Lead 3, 37.8%. (These figures indicate percentage of the entire number of cases showing this abnormality.) In some patients all leads were involved while in others, various combinations of the 4 leads showed involvement.

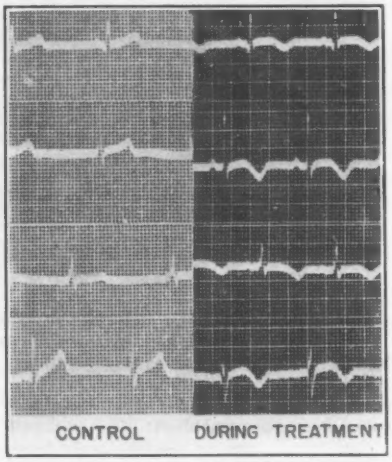

FIG. 3.—Electrocardiographic changes during administration of tartar emetic. "Control" record taken prior to treatment. "During Treatment" record taken 48 hours after last injection of 28 cc. 0.5% solution tartar emetic. Total dose 1.8 gm. (see text for schedule of administration). Note increase in height of P_2 and T wave inversion in all leads. Marked prolongation of QT interval (0.523; control 0.408).

T Waves. It was in this component of the electrocardiogram that the most striking changes during antimony therapy occurred. These consisted of a decrease in amplitude of T waves in all leads, producing in a considerable number of patients diphasic or inverted T waves. Such changes were found to occur in 99% of the patients in this study. In order to classify the records as to degree of change caused by antimony, the actual

millimeter change in T-wave amplitude from the control records was measured to the nearest 0.5 mm. in Leads 1, 2, 3 and 4, and these were totalled for each patient. The range of this total change was from 0 to −21 mm.; 31% of patients showed a total change from −0.5 to −5 mm., 41% from −5.5 to −10 mm., 23% from −10.5 to −15 mm., and 4% from −15.5 to −21 mm. Typical T-wave changes are shown in Figures 1, 2 and 3.

Graybiel *et al.* in their excellent article[4] have published percentage distribution curves on the amplitude of T waves in their 1000 young healthy aviators. Comparison of these with similar percentage distribution curves made on 100 control records taken on our patients before therapy reveal good correlation. The mean T-wave amplitudes of their 1000 cases were

study in Column 2. In Column 3 are the mean T-wave amplitudes of the records of our patients showing the maximum observed effect of antimony therapy, and in Column 4 the percentage change.

Figure 4 shows the frequency distribution curves in each lead before and during therapy. Solid lines represent control records and broken lines records taken during therapy. In each case the records chosen during therapy were those showing the maximum observed change but do not necessarily indicate the maximum change which occurred, since, as stated previously, the greatest antimony effect was frequently missed because of improper timing of the electrocardiogram during the course of treatment. Decreases in amplitude of the T waves are shown by a shift of the broken line curve to the left, *i. e.*, to the lower position on the

TABLE 1.—COMPARISON OF MEAN T-WAVE AMPLITUDE IN 1000 NORMAL SUBJECTS AND 100 PATIENTS BEFORE AND DURING ANTIMONY THERAPY

	1000 normal subjects (4)	100 patients		Decrease (%)
		Before antimony	During	
Lead 1 . . .	+2.55 mm.	+2.26 mm.	+0.88 mm.	59.4
Lead 2 . . .	+3.32 mm.	+3.17 mm.	+0.80 mm.	74.8
Lead 3 . . .	+1.33 mm.	+1.03 mm.	+0.04 mm.	103.9
Lead 4 . . .	+1.33 mm.	+4.93 mm.	+2.36 mm.	52.2

Lead 1 +2.55 mm., Lead 2 +3.32 mm. and Lead 3 +1.33 mm., as compared with our mean amplitudes of +2.26 mm. in Lead 1, +3.17 mm. in Lead 2 and +1.03 mm. in Lead 3. This favorable comparison indicates that the patients in this study comprise a fairly representative group of normals and establishes the fact that infection of these patients with schistosomiasis has, in itself, no effect on their electrocardiograms. Further, the fact that the mean amplitude of the T waves in our control records is within the range of normal indicates that antimony treatment which all patients had received from 1 to 3 months previously had no lasting effect on the T wave.

Table 1 shows a comparison of the mean amplitude of T waves of the 1000 cases analyzed by Graybiel *et al.* in Column 1 and of the 100 control records in this

scale, thus forming a definitely abnormal frequency distribution curve for records during therapy.

Changes in T-wave contour other than flattening of the peaks occurred in 24% of the cases in this study. These changes consisted of notching of the T waves and occurred most frequently in Lead 4, occasionally in Leads 1 and 2 and rarely in Lead 3. Observation of the development and progression of this abnormality in serial records taken on the same patient during treatment affords an interesting clue as to the method of T-wave inversion in Lead 4 due to antimony. It was frequently observed in this lead that initially a notch appeared late in the T deflection, which in subsequent records became deeper, eventually descending below the iso-electric line to produce a + diphasic T_4, and finally with the complete disap-

pearance of positive deflection to form a deeply inverted T_4. This apparent sequence of changes was never observed in the limb leads, even though some records showed deeply inverted T waves in all leads.

electrocardiographc changes persisted, a total of 109 records taken from 1 to 86 days after treatment were analyzed. From this analysis it was found that there existed such a wide variation in the persistence of changes that no definite con-

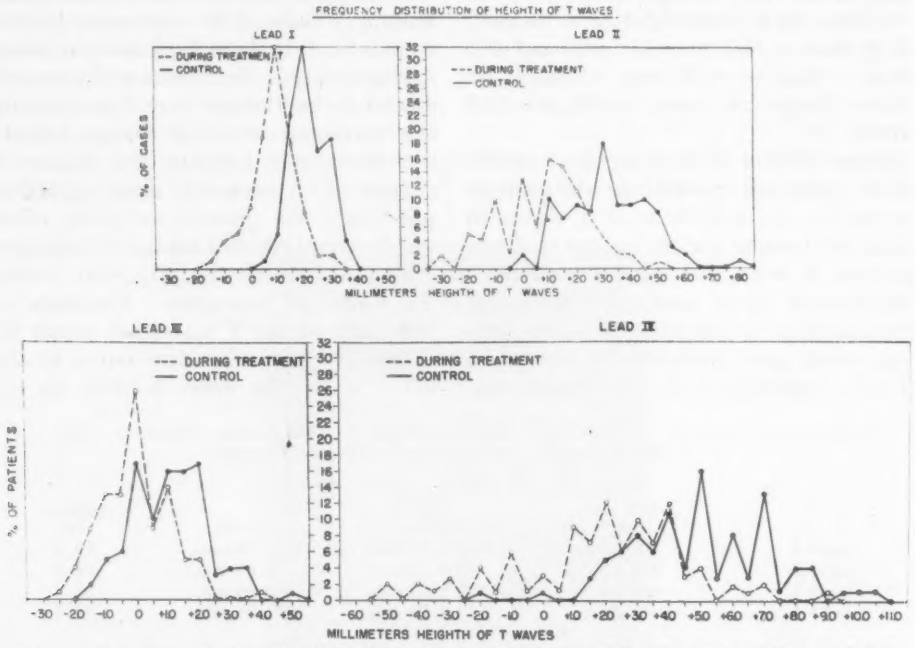

FIG. 4.—Frequency distribution in height of T waves in electrocardiograms taken before and during treatment with antimony in 100 patients. Note shift of treatment curve to left indicating frequency of decrease in amplitude or inversion of T waves in all leads during the administration of antimony. (For discussion see text.)

NOTE.—One patient had a control record with an inverted T_4. He had completed 40 cc. of fuadin 60 days prior to the taking of this record. His electrocardiogram was otherwise within normal limits.

On a few patients, frequent electrocardiograms were taken before, during and after injections in various periods during therapy. From these studies it was apparent that T-wave changes occurred gradually and progressively throughout the course of therapy. The earliest changes appeared after the first, second or third injection, and reached the maximum at or near the end of treatment. There was no tendency towards fluctuation from day to day nor was any regression towards normal observed during the 48 hour period between injections.

In attempting to determine how long after cessation of antimony therapy the clusions could be drawn. Thirteen records were taken on different patients from 37 to 49 days after therapy and of these 6 had T waves equal in height to control levels, an additional 4 showed less than 30% of the original maximum change still remaining, while in 3 records 50 to 75% of the total observed change still persisted. Between 52 and 67 days after therapy complete return to normal was observed in 9 out of 15 records. Less than 25% of the total change still persisted in 4 records, and in the remaining 2 records 50 and 56% of the original total T-wave change was still present. In approximately 10% of these post-treatment

records the T waves returned to levels exceeding those of the control record. This curious change was noted in electrocardiograms taken on different patients from 18 to 78 days after cessation of treatment. No correlation was found between persistence of T-wave changes and the type or dosage of antimony treatment given. No attempt will be made to explain these results, other than to say that the major factor is apparently an individual variation about which we know little.

devised to correct for this variation. In this study "corrected Q–T" was calculated by the formula $Q\text{–}T = K\sqrt{RR}$ as advocated by Cheer and Dieuaide[2] in 1931. The mean "corrected Q–T" of all control records was 0.396 as compared with a mean of 0.422 for those records showing maximum antimony effect.

In addition, Q–T was plotted graphically against the cycle length, RR, as shown in Figure 5. In this graph the parallel lines representing the range of normal are those used by Feil[3] in his

TABLE 2.—COMPARISON OF CHANGES IN AMPLITUDE OF T WAVES DURING TREATMENT WITH VARIOUS AMOUNTS OF FUADIN AND TARTAR EMETIC

Total change (mm.)	T.E. 1.45 gm. (41 patients)	T.E. 1.8 gm. (21 patients)	Fuadin 70 cc. (31 patients)	Fuadin 100 cc. (7 patients)
0 to − 5	24.4%*	19.0%	42.0%	71.4%
− 5.5 to −10	51.2%	38.1%	35.5%	14.3%
−10.5 to −15	17.0%	38.1%	22.5%	14.3%
−15.5 to −21	7.4%	4.8%	0	0
Mean total change	−8.4 mm.	−8.8 mm.	−6.9 mm.	−4.6 mm.

* % in all instances represents % of total patients treated in each schedule.

Early in the course of this study, certain impressions were reached concerning the comparative effects of tartar emetic and fuadin on the electrocardiogram. Table 2 shows a classification of patients on different treatment schedules with regard to degree of total change produced by this treatment on the T waves in all leads. It must be remembered that these data are limited by the fact that the maximum change was not recorded in every case. In spite of this limitation it is obvious that tartar emetic has a greater effect on the electrocardiogram than does fuadin and that in the case of the former the larger the total as well as the daily dosage the greater the T-wave change. The disproportion between electrocardiographic effect and dosage of fuadin is due to (*a*) the limitation mentioned above and (*b*) to the fact that in this study adequate records were available in only 7 patients treated with 100 cc. of fuadin.

ELECTRICAL SYSTOLE. Variation of the Q–T interval with changes in heart rate has long been recognized by many investigators, and several formulæ have been

paper on electrocardiograms and cardiac systole in pellagra. Control values are represented by solid circles and values during antimony therapy by open circles. Abnormally prolonged Q–T intervals occurred in 7% of the control records as compared with 27% of the records taken during treatment. Further analysis of the records showing prolongation of the Q–T interval reveals them to be proportionately distributed in relation to the treatment schedule used. This change is apparently caused with equal frequency by either fuadin or tartar emetic, and no significant difference was found between the different dosage schedules used in this study. In most cases, records with prolonged Q–T intervals also showed pronounced T-wave changes, although many patients with markedly lowered T waves had normal Q–T intervals. The mechanism of this increase in the duration of electrical systole is unknown.

PENTAVALENT ANTIMONY. On a few patients with leishmaniasis and filariasis, complete electrocardiographic studies were made during treatment with pentavalent

antimony compounds. Drugs used were neostibosan and stibanose. Patients on this class of antimony compounds showed similar changes to those seen with trivalent antimony, but to a much less marked degree. Indeed, some patients showed no changes whatsoever in electrocardiograms taken during treatment.

changes, but in 2 others showing equally marked T-wave changes, there was no slowing of the pulse. In only 2 instances did the heart rate of our patients fall below 60 beats per minute during treatment, 1 having a rate of 59 on the last day of therapy and the other a rate of 51 4 days after completion of therapy. In

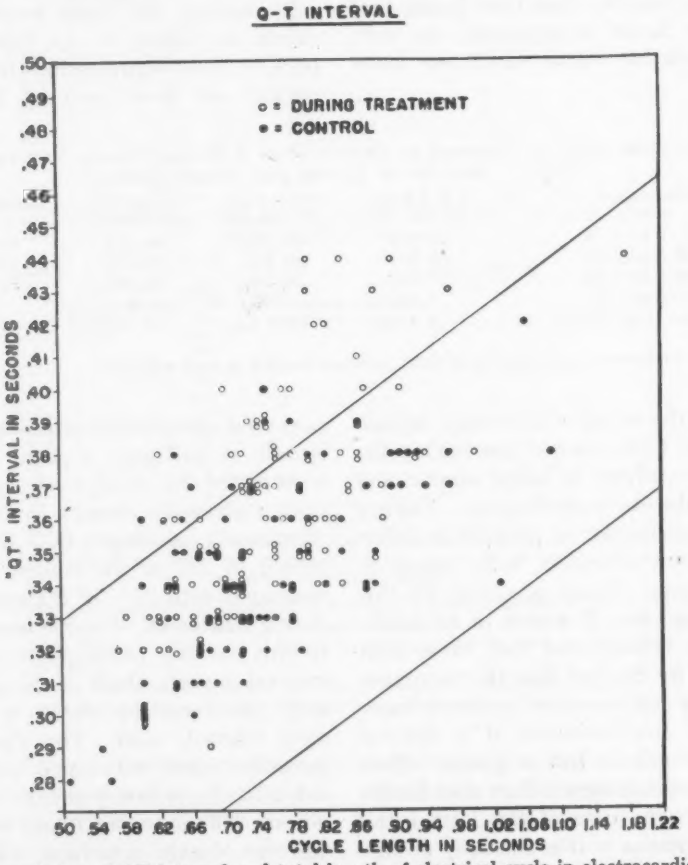

FIG. 5.—Correlation of QT interval and total length of electrical cycle in electrocardiograms taken before and during treatment with antimony in 100 patients. Note that 27% of patients during treatment exhibit prolongation in the QT interval. Normal range indicated by parallel lines (6).

Discussion. In this study the absence in the heart rate during antimony therapy is contrary to the findings of numerous other investigators, who frequently describe a pronounced bradycardia. Mainzer and Krause[5] found a decrease in the heart rate in some of those cases showing the most marked electrocardiographic

many cases showing marked changes in other phases of the electrocardiogram there was actually an increase in the heart rate. In 2 patients, records taken before, during and after the actual injection of tartar emetic showed a slight increase in heart rate.

In our study, no attempts were made

to ascertain the underlying causes of these electrocardiographic changes. No lesions are found in the myocardium of dogs who die during the administration of large amounts of antimony.[1] The transient nature of the electrocardiographic changes with complete return to normal after varying periods is certainly presumptive evidence against the existence of actual myocardial damage. The fact that under close observation none of our patients developed any clinical signs or symptoms referable to the heart despite unlimited physical activity, except for 30 minutes bed-rest immediately following each injection, is additional evidence in this direction.

Mainzer and Krause[5] discuss vagus stimulation as a possible explanation for antimony effect on the electrocardiogram principally because of bradycardia. However, those authors are not impressed by this explanation. The absence of significant change in the heart rate as found in this study also raises a valid objection to the autonomic theory, since it is well known that the rate is very sensitive to changes in autonomic balance. In addition, the persistence of electrocardiographic changes for as long as 60 days after the cessation of treatment and the absence of other signs of antimony effect upon the nervous system, both, cast considerable doubt upon an autonomic etiology.

Winkler *et al.*[8] have studied the effect of increased potassium ion concentration upon the electrocardiogram in dogs. They consistently found an increase in T-wave amplitude and lowering and eventual disappearance of P waves, as the serum potassium concentrations rose. Since these changes are just the opposite from those observed in this study, it seems logical to conclude that the potassium ion present in tartar emetic is not an etiologic factor in the electrocardiographic changes described in this paper.

Since the underlying mechanism producing these changes is at present unknown, their significance cannot definitely be established. However, it is our opinion that this is a relatively harmless side action of antimony, transient in nature, and of no great import as to impairment of cardiac function or as to prognosis of the patient. With the expected increase in use of antimony compounds in the next few years, it is of the utmost importance that these changes be recognized and their significance known, so that mistaken diagnoses of cardiac disease be avoided.

Summary and Conclusions. 1. An analysis was made of 315 electrocardiograms taken on 100 patients during various stages of treatment with tartar emetic and fuadin for schistosomiasis infection.

2. An increased amplitude of P waves in Leads 2 and 3 was found in 11% of the patients.

3. A fusion of ST segment and T waves was found in 45% of the patients.

4. Varying degrees of decrease in amplitude of T waves in all leads, resulting in deep inversion in many cases, were found in 99% of the patients. This change was more pronounced during tartar emetic treatment than during fuadin treatment.

5. The Q–T interval was prolonged beyond the limits of normal in 27% of the patients in this study.

6. The duration of these changes is variable, and has been noted up to 2 months after cessation of treatment.

7. The etiology and significance of these changes are unknown. It is our opinion that they represent a transient side action of antimony not indicative of cardiac damage or serious impairment of cardiac function.

8. Recent antimony therapy must be considered in evaluating abnormal electrocardiograms found in veterans and others.

REFERENCES

1. Brady, F.: National Institute of Health, Div. of Zool., Bethesda, Md.: Personal communication.
2. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole ("Q–T" Interval) of the Heart, J. Clin. Invest., **10**, 890, 1931.

3. Feil, H.: A Clinical Study of the Electrocardiogram and of the Phases of Cardiac Systole in Pellagra, Am. Heart J., **11**, 173, 1936.

4. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1000 Young Healthy Aviators, Am. Heart J., **27**, 524, 1944.

5. Mainzer, F., and Krause, M.: Changes of the Electrocardiogram Appearing During Antimony Treatment, Trans. Roy. Soc. Trop. Med. and Hyg., **33**, 405, 1939.

6. New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Tuberculosis and Health Assn., New York, 1942.

7. Tarr, L.: Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram, Bull. U. S. Army Med. Dept., **5**, 336, 1946.

8. Winkler, A. W., Hebbel, E. H., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Phys., **124**, 2, 1938.

THROMBOSIS AND EMBOLISM OF PULMONARY VESSELS WITH SPECIAL REFERENCE TO PULMONARY VEIN THROMBOSIS

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Recent reports on the use of such anticoagulants as dicumarol and heparin in the various thrombotic and embolic states and the recent advances in the diagnosis, localization and treatment of phlebothrombosis in the lower extremities have awakened tremendous interest in the entire subject of thrombosis and embolism. For this reason a survey was undertaken based on the postmortem material observed at Bellevue Hospital. The purpose is to present the incidence of pulmonary emboli, thrombi and infarcts, their most frequent sources, the usual underlying disease entities that are present and the nature and evolution of the infarcts themselves. Such related questions as pulmonary venous thrombosis as a source of both bland and septic infarcts and the incidence of pulmonary systemic emboli in myocardial infarction were also studied.

In a series of 1000 consecutive postmortem examinations on patients over the age of 20, excluding cases of subacute and acute bacterial endocarditis and deaths due to trauma, 109 (10.9%) were found to have pulmonary thrombi or emboli. Of these 109 cases, 84 (8.4% of total amount) had infarcts of the lung (Table 1). This latter figure is in agreement with the incidence generally reported. The majority of these patients were over the age of 50 with the peak incidence at the age of 60. There were no significant sex differences. It should be mentioned that very few surgical cases (postoperative) are represented in this series.

Two hundred consecutive necropsied cases in which pulmonary emboli were found (some not in original series) were analyzed to determine the source of these emboli. Of these, 61 had thrombosis in the systemic veins, mainly the femoral and saphenous. Other venous sites were pelvic, lumbar, axillary, jugular and inferior vena cava. Mural thrombi in the right side of the heart were revealed in 55 cases (48 in the right auricle, 7 in the right ventricle). In the remaining 84 cases the site of the thrombosis was undetermined but was most likely located in the deep veins of the lower extremities, since none was found in the heart and permission was not granted for adequate dissection of the leg veins. It is also possible that in some of these undetermined cases, the vascular obstruction resulted from thrombi within the pulmonary arterial tree rather than from emboli. This may have been so especially in those cases with rheumatic heart disease. If these latter 84 cases are considered together with the known 64 cases containing systemic venous thrombi, there results a combined total of 148 cases in which the source for the emboli was extracardiac as compared to 55 cases in which the source of the emboli probably originated from within the heart (Table 2).

In a study undertaken by Hunter *et al.*[1] in which the leg veins were dissected in 350 consecutive necropsies, it was revealed that 52.7% had thrombi in the leg veins. In this series there were no significant sex differences; the average age was 59.78 as compared in 64.9 in those cases that did not have thrombi. This is an insignificant difference. In those cases having leg vein thrombi, 51 had pulmonary emboli; of these latter cases death was apparently due to pulmonary emboli

in 11 instances. The high frequency of thrombosis of the veins of the lower extremities is not generally recognized, particularly in view of the fact that in the great majority of the cases the first clinical evidence of their presence are manifestations of an embolus in the lungs. Hunter's[4] figures are all the more significant because they are minimum figures, for in many of their cases it was impossible for them to perform as adequate a dissection of the lower extremities as they desired.

of systemic emboli in 48.7% cases. The incidence of embolic manifestations in these cases was about 3 times as great as in those cases in which mural thrombi were not present in the heart. One hundred consecutive necropsies (Bellevue Hospital series) of cases with pulmonary infarcts were compared with a series of 50 necropsied cases in which pulmonary emboli were present without infarcts (Tables 3 and 4). In the 100 cases with pulmonary infarcts it was found that 82 had heart disease, in 16 no heart disease

TABLE 1.—INCIDENCE OF PULMONARY ARTERIAL EMBOLI AND INFARCTS

Number of cases	1000
Number of infarcts	84 (8.4%)
Number with emboli without infarcts	25 (2.5%)
Total	109 (10.9%)

TABLE 2.—SOURCE OF EMBOLI IN PULMONARY ARTERIAL EMBOLIZATION AND INFARCTION

Number of cases	200
Systemic veins	61
Heart—Right auricle	48
Right ventricle	7
Undetermined	84

Thrombi in the axillary veins are an infrequent source of emboli in the lung. According to the review by Veal,[10] in 1935, only 150 cases of axillary vein thrombosis had been reported during the preceding 50 years. However, in recent years many additional reports have appeared. Veal[10] classifies thrombosis of the axillary veins under 2 groupings—primary, caused by trauma or bacterial infection, and secondary, usually due to malignant tumors of the chest region. Although axillary vein thrombosis is present it is an uncommon source of pulmonary emboli.

The frequency of intercardiac mural thrombi, especially in cardiac patients, as a source of both pulmonary and systemic emboli was well illustrated in a report by Garbin.[3] In a study of 771 consecutive necropsies on patients with heart disease, 161 had mural thrombi in the chambers of the right side of the heart. Of these, 57.8% were associated with pulmonary infarcts; 193 cases had thrombi in the left side of the heart, that were the source

was present, the patients having died of a variety of diseases, such as carcinoma, tuberculosis, etc. However, the situation was quite the reverse in those cases having pulmonary emboli without infarction of the lung. In 50 such cases, 34 had no evidence of heart disease. This merely confirms the well-known fact that the combination of chronic passive congestion and obstruction of the pulmonary arteries is usually necessary before infarction will take place. However, this is not always necessary, as we have seen pulmonary emboli produce infarcts in the lungs in patients who do not have heart disease or any evidence of circulatory failure and who were not confined to bed.

Further study of the 100 cases with pulmonary infarcts with reference to the existing disease revealed that arteriosclerotic heart disease with or without hypertension was present in 34 cases. In these 34 cases, the source of the emboli was in the right auricle 10 times, the leg veins 10 times, and undetermined 14 times; 21 cases had arteriosclerotic heart disease

with either recent or old myocardial infarcts; of these the source of emboli in the lungs was the right ventricle in 3 instances, right auricle in 7, leg veins in 3, and undetermined in 8 cases. Of 20 patients with rheumatic heart disease, the source of emboli was in the auricle 11 times, leg veins once, and undetermined in 8 cases. Syphilitic heart disease with valvular involvement was present 5 times; periarteritis nodosa was present once; 18 patients did not have any cardiac disease (Table 5).

that serosanguineous pleural fluid was present in 13 of 100 instances of pulmonary infarction. Serous fluid was present 34 times and no fluid at all in the remainder. When the pleural fluid could be with certainty attributed to the inflammation of the pleura resulting from the infarct, it was invariably found to be blood-tinged. In all of these instances the fluid was usually scant in amount and rarely exceeded several hundred cubic centimeters. In each instance when serous fluid was present, some degree of

TABLE 3.—UNDERLYING DISEASE IN 100 CASES OF PULMONARY ARTERIAL EMBOLI WITH INFARCTS

Arteriosclerotic and hypertensive heart disease	34
Arteriosclerotic and hypertensive heart disease with myocardial infarcts	21
Rheumatic heart disease	20
Syphilitic heart disease	5
Periarteritis nodosa	1
Non-cardiac disease	18

TABLE 4.—UNDERLYING DISEASE IN 50 CASES OF PULMONARY ARTERIAL EMBOLI WITHOUT INFARCTION

Non-cardiac disease	34
Cardiac disease	16

TABLE 5.—SOURCE OF PULMONARY ARTERIAL EMBOLI IN VARIOUS CARDIAC CONDITIONS

Type.	Auricle.	Ventricle.	Systemic veins.	Undetermined.
Arteriosclerotic and hypertensive heart disease	10	0	10	14
Arteriosclerotic and hypertensive heart disease with myocardial infarct	7	3	3	8
Rheumatic heart disease	11	0	1	8

It may be noted that thrombi in systemic veins as a source of pulmonary emboli are more frequent in arteriosclerotic heart disease than in rheumatic heart disease. This may be accounted for partially by the fact that arteriosclerotic heart disease occurs in the older age group and also that in some instances pulmonary infarcts and rheumatic heart disease may result from local pulmonary thrombosis rather than embolization.

The question of the clinical diagnosis of pulmonary infarcts at times presents great difficulties. For this reason the location, frequency and the fate of the infarcts, as well as the character of the pleural fluid associated with them was studied to determine whether these anatomic findings may be of aid in the clinical differential diagnosis. It was found

heart failure, edema and very often ascites existed. Therefore, the presence of this serous fluid could not be directly attributed to the effect of the pulmonary infarct on the pleura. As to the location of the pulmonary infarcts, it was found that they occur twice as frequently in the lower lobes as in the upper lobes. It was also noted that multiple infarcts are twice as frequent as a single infarct. There were no significant sex differences.

The fate of a pulmonary infarct was carefully studied by Castleman.[2] He combined roentgenographic studies with anatomic observations and found that infarcts gradually become replaced by fibrous tissue and shrink down to such an extent that they end as a fine, almost unobservable, fibrous scar. Very few of the pulmonary infarcts undergo liquefac-

given for those circumstances (paradoxical embolus), whereby emboli are said to pass through a patent foramen ovale under normal conditions, is not physiologically sound. The normal pressure in the left auricle is greater than that of the right; consequently an embolus would not pass from the right to the left auricle. However, under unusual circumstances the presence of a patent foramen ovale might account for a so-called paradoxical embolus. Such instances of paradoxical embolus can occur when a patient has first had preceding emboli in the pulmonary arteries resulting in pulmonary hypertension. The pressure in the right auricle has, therefore, become increased and any subsequent embolus would then be able to pass through a patent foramen ovale from the right auricle to the left auricle and give rise to systemic embolization.

Pulmonary venous thrombi are not as frequent as those in the systemic veins because the lung is in constant motion, it is protected from trauma by the bony chest cage and the veins are on the same general level with the heart, therefore, not necessitating the support of a long column of blood. Nevertheless, if more careful search were routinely made, undoubtedly more examples of pulmonary venous thrombi would be found.

Although not concerned with the main subject of this report, it was noted that in over 5000 postmortem examinations, pulmonary thrombophlebitis as a source for systemic emboli occurred in only 1 instance. In a review of the recent literature, we were only able to find reference to 1 similar case (Melbourne[9]). A pulmonary thrombophlebitis in the case noted in our series was secondary to a large lung abscess. Many infected systemic emboli were present. It is not obvious why the lung that is so frequently the site of pyogenic infections should infrequently be the source of infected emboli.

Conclusions. The general incidence of pulmonary emboli or thrombi in a series of 1000 consecutive necropsies (not inclusive of bacterial endocarditis and traumatic cases) was 10.9%.

The source of emboli in the lung is approximately twice as frequent from the systemic veins as from thrombi within the heart.

Pulmonary emboli in patients without heart disease frequently do not cause pulmonary infarcts.

In 100 consecutive necropsied cases of myocardial infarction, pulmonary emboli were noted 36 times and systemic arterial emboli 25 times. The incidence of pulmonary emboli is much greater in association with recent myocardial infarcts than with healed infarcts. The pulmonary emboli very often contributed to the death of the individual.

Pulmonary venous thrombi as a source of systemic arterial emboli occur more frequently than is generally recognized. Pulmonary tuberculosis was the disease most often associated with pulmonary venous thrombi.

Infected emboli resulting from pulmonary thrombophlebitis are exceedingly rare.

REFERENCES

1. Brenner, O.: Pathology of Vessels of Pulmonary Circulation, Arch. Int. Med., **56**, 211, August; 457, September; 724, October; 976, November; 1189, December, 1935.

2. Castleman, B., and Hampton, A. O.: Use of Post-mortem Chest Teleoroentgenograms in Pathologic Examination of Lungs With Special Reference to Pulmonary Infarcts, J. Tech. Methods, **21**, 5, 1941.

3. Garvin, C. F.: Mural Thrombi in Heart as a Source of Emboli, Am. J. Med. Sci., 201, 412, 1941.

4. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of Deep Veins of the Leg, Arch. Int. Med., **68**, 1, 1941.

5. Hussey, H. H., and Katz, S.: Septic Pulmonary Infarction—Report of Eight Cases, Ann. Int. Med., **22**, 526, 1945.

6. Medlar, E. M.: Early Cardiac Infarction Caused by Embolus of Caseous Tuberculous Material—Report of a Case, Am. J. Path., **11**, 707, 1935.

7. Neel, W., and Herrmann, L. G.: Tuberculous Peripheral Arteritis Associated With Tuberculous Thrombophlebitis in Lungs, Am. Heart J., **22**, 702, 1941.

8. Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. Am. Med. Assn., **130**, 398, 1946.

9. Royal Melbourne Hospital Clinical Reports: Thrombophlebitis of Pulmonary Veins, **12**, 25, 1941.

10. Veal, J. R.: Thrombosis of Axillary and Subclavian Veins, Am. J. Med. Sci., **200**, 27, 1940.

RHEUMATOID ARTHRITIS

I. Introduction to a Study of Its Pathogenesis*

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The medical imagination has long been hypnotized by the notion that infection is in some way responsible for rheumatoid (atrophic) arthritis. This impression has largely been based upon confusion with the type of arthritis which is metastatic from a focus of infection, upon superficial resemblances between rheumatoid arthritis and infectious processes and upon certain serologic observations.

Typical Rheumatoid Arthritis. It cannot be too strongly emphasized that the papers which follow are applicable only to *true* rheumatoid arthritis, a disease state which has been described by many authorities as a recognizable syndrome, if not an entity. In order that there be no misconception in the mind of the reader, its most characteristic clinical features are recapitulated as follows: a gradual onset between the ages of 20 and 40; a predilection for thin females living in a temperate climate; a fairly symmetrical involvement of the extremities, particularly knees, wrists and proximal interphalangeal joints of fingers by an indolent, painful, tender, somewhat doughy, fusiform swelling with more of local heat than redness; and the gradual development of deforming contractures through a series of remissions and exacerbations until the advent of bony or fibrous ankylosis brings the pain to a close. It should be axiomatic that (hypertrophic) osteoarthritis deviates from this clinical pattern in so many respects (to say nothing of roentgenographic and gross pathologic differences) that its status as a separate disease is clear. Other types of arthritis which for the sake of clarity will be omitted from present consideration include Still's disease, the ankylosing spondylitis of Marie-Strümpell, Felty's syndrome, "menopausal" arthritis, "psoriatic" arthritis, and arthritis secondary to a focus of infection.

In selecting cases of rheumatoid arthritis for serologic study we have used the following criteria: disease duration of at least a year and a fairly symmetrical involvement of proximal interphalangeal joints of fingers. The "activity" of the disease process was disregarded.

Arthritis From Focal Infection. In synovitis attributable to a focus of infection, it is assumed that bacterial toxins and not the bacteria themselves are carried to the joint in the blood stream. Such metastatic toxins probably have no "arthrotropic" intentions. It is rather that the joints respond selectively to the presence of the toxins in the general circulation because, as large tissue spaces[1] endowed with an abundant blood and nerve supply, they are physiologic sounding boards. It is for this reason that the synovial reaction is a dominant feature of such systemic disturbances as the antigen-antibody interactions occurring in rheumatic fever during the acute phase (*cf.* Coburn and Pauli[6]) or in serum disease. Once a synovial reaction to a substance arriving *via* the blood stream has become established it tends to become more intense because a local increase in capillary permeability permits the deposition of still larger amounts of the causative agent (*cf.* Menkin[14]). Arthritis due to metastatic toxin will thus be no more symmetrical

* The series of papers of which this is the first has been supported by grants from the Charlotte Drake Cardeza Foundation of the Jefferson Medical College and the National Foundation for Infantile Paralysis, Inc.

than are the joint lesions of rheumatic fever, and its only characteristic feature will be its response to alterations in the foci of infection. Typical examples observed for a sufficient time present a clear distinction between rheumatoid arthritis and arthritis which is metastatic from a focus of infection. The latter is restored toward normal when the focus subsides, and the former is either unaccompanied by demonstrable foci or uninfluenced by their treatment. Atypical cases, of course, are confusing and it is possible that both types may coëxist in the same patient or even in the same joint. The present discussion is concerned only with those cases of rheumatoid arthritis which approximate the syndrome described above as "typical."

An open-minded approach to the baffling problem of the pathogenesis of rheumatoid arthritis must be unhampered by the traditional concept of a bacterial etiology. Although resting on insecure evidence, this concept has persisted strongly and has been the greatest single obstruction to a solution of the problem.

The Theory of Bacterial Etiology. A brief inspection of the foundation of the bacterial theory will help to place it in its proper perspective. It had its origin in an era of enthusiasm for assigning infectious causes to diseases. It was fostered by the presence of external signs of inflammation accompanied by an increased rate of erythrocyte sedimentation, and it was strengthened by observation of patients in whom a frank focus of infection was undeniably related to arthritis. It was subsequently buttressed when a similar arthritis was produced in experimental animals by bacterial injections and in many minds it was conclusively established by the demonstration of strong agglutinins for the hemolytic streptococcus in the serum of many patients with typical rheumatoid arthritis.

These various lines of evidence, however, will not bear close scrutiny. Inflammation does not necessarily signify infection, as the signs and symptoms in gout or fresh burns will bear witness; nor does a rapid sedimentation rate necessarily signify infection, as observations[10] of an increased rate in gout will testify. The fact that focal infection can cause arthritis does not mean that all non-specific arthritides have the same cause. The experimental argument loses weight when we consider that turpentine injections are capable of arousing an arthritis which grossly and microscopically closely resembles that produced by injections of bacteria.[5] The significance of the streptococcus agglutinins will be discussed in a subsequent paper.

Arguments Against a Bacterial Origin. The presence of bacteria of any species has not been consistently demonstrable in the blood of patients with rheumatoid arthritis.[12] The extraordinary prolongation of the active stage of the joint lesions in this disease and their tendency to symmetry are arguments against bacterial etiology in general, and their indifference to sulfanilamide[7] and penicillin[3,8] is against a streptococcal etiology in particular.

Antistreptolysins and Antifibrinolysins. Antibodies formed in response to the presence of the whole hemolytic streptococcus may be expected to be directed not only against the different fractions which comprise its complex structure but also against the toxins or products of the microörganism. Thus, known hemolytic streptococcal infections such as scarlet fever or erysipelas or presumed hemolytic streptococcal infections as rheumatic fever ordinarily arouse antibodies which oppose the action of streptococcal hemolysin (antistreptolysin) and streptococcal fibrinolysin (antifibrinolysin). In rheumatoid arthritis these antibodies have not been found in significant titer.

The first report on antistreptolysin in the serum of rheumatoid arthritis was that of Myers and Keefer[15] who stated that it was not present in excess of normal. Dawson and Olmstead[9] found no definite increase in antistreptolysin in cases of more than 1 year's duration but recorded

some increase in earlier cases. Slight increases in a few cases were reported by Blair and Hallman[2] and by McEwen, Bunim and Alexander,[13] but the levels found were not comparable with those in rheumatic fever and known hemolytic streptococcal infections. Discrepancies in these observations may be accounted for by variations in selection of cases, different criteria for a normal level and disregard of antecedent upper respiratory tract infections. In 1940 Bunim and McEwen[4] concluded that antistreptolysin is not increased in rheumatoid arthritis. With regard to antifibrinolysin, Myers, Keefer and Holmes,[16] McEwen, Bunim and Alexander,[13] and Perry[17] are in agreement that rheumatoid arthritis sera are within normal limits.

Reports of attempts to demonstrate complement-fixing antibodies and cutaneous reactions to streptococcus fractions in rheumatoid arthritis have been summarized by Hench[11] as contradictory and inconclusive.

Summary. The importance of the distinction between true rheumatoid (atrophic) arthritis and arthritis of other types, particularly that which is secondary to a focus of infection, is emphasized.

The foundations of the bacterial theory, and more specifically, the hemolytic streptococcal theory, of the origin of rheumatoid arthritis are examined and found insecure.

REFERENCES

1. Bauer, W., Ropes, M. W., and Waine, H.: Physiol. Rev., **20**, 272, 1940.
2. Blair, J. E., and Hallman, F. A.: J. Clin. Invest., **14**, 505, 1935.
3. Boland, E. W., Headley, N. E., and Hench, P. S.: J. Am. Med. Assn., **126**, 820, 1944.
4. Bunim, J. J., and McEwen, C.: J. Clin. Invest., **19**, 75, 1940.
5. Cecil, R. L., Angevine, D. M., and Rothbard, S.: Am. J. Med. Sci., **198**, 463, 1939.
6. Coburn, A. F., and Pauli, R. H.: J. Exp. Med., **69**, 143, 1939.
7. Coggeshall, H. C., and Bauer, W.: New England J. Med., **220**, 85, 1939.
8. Comroe, B. I.: Am. J. Med. Sci., **209**, 646, 1945.
9. Dawson, M. H., and Olmstead, M.: Proc. Soc. Exp. Biol. and Med., **34**, 82, 1936.
10. Haden, R. L., and Kinell, J.: J. Lab. and Clin. Med., **27** 725, 1942.
11. Hench, P. S.: A Survey of Chronic Rheumatic Diseases, Oxford Univ. Press, p. 35, 1938.
12. McEwen, C., Alexander, R. C., and Bunim, J. J.: J. Lab. and Clin. Med., **21**, 453, 1936.
13. McEwen, C., Bunim, J. J., and Alexander, R. C.: J. Lab. and Clin. Med., **21**, 465, 1936.
14. Menkin, V.: Am. J. Med. Sci., **190**, 583, 1935.
15. Myers, W. K., and Keefer, C. S.: J. Clin. Invest., **13**, 155, 1934.
16. Myers, W. K., Keefer, C. S., and Holmes, W. F., Jr.: J. Clin. Invest., **14**, 119, 1935.
17. Perry, C. B.: Ann. Rheum. Dis., **2**, 147, 1940.

RHEUMATOID ARTHRITIS

II. Non-specific Serologic Reactions*

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In the course of a study of precipitins in the sera of patients with rheumatoid (atrophic) arthritis, to be reported in subsequent papers, peculiar non-specific properties were noted in the sera. These properties appear to exert an influence of primary importance on the general serology of this disease.

Precipitation With Physiologic Salt Solution. The "negative" or "saline control" tube of each precipitin test contained 0.4 cc. of 0.85% sodium chloride solution, 0.1 cc. of serum and no antigen. Each test was incubated in a water bath at 37° C. for 2 hours and refrigerated overnight before being examined. The sera of many patients with typical[6] rheumatoid arthritis of more than 1 year's duration have a tendency to precipitate in this "negative" control tube. Before centrifugation, the precipitate may often be seen (with a reading glass, fluorescent lamp, dark background and darkened room), appearing as fine particles resembling those of a genuine antigen-antibody reaction. Like the latter, their intensity increases day by day as the period of observation is prolonged. With centrifugation, the tendency of arthritis serum to precipitate in saline becomes still more marked. The precipitate is now apt to take the form of flakes, visible with the unaided eye. These likewise resemble the flakes of an antigen-antibody reaction, except that the arthritis serum flakes are occasionally more translucent. Of the control sera, from patients with diseases other than rheumatoid arthritis, a few have shown fine particles in the saline control before centrifugation, visible only with the reading glass, but none have been encountered which yielded flakes on centrifugation. The uncentrifuged non-specific precipitation of arthritis serum increases with the age of the serum used in setting up the test. Usually it is not well marked until the serum has stood in the refrigerator for about 1 week. It is not abolished by fasting the patient overnight before drawing blood. The centrifuged non-specific precipitate is less influenced by the age of the serum. Its intensity bears only a general, not a closely quantitative relation to that which occurs before centrifugation. With the passage of time there is also apt to be some spontaneous precipitation in the refrigerated stocks of undiluted serum, a possible source of error in precipitin testing. Precipitation in the saline controls of arthritis serum precipitin tests after centrifugation has been recorded by Dawson, Olmstead and Jost[4] and by Chasis and McEwen,[2] but its importance does not seem to have been recognized.

Furthermore, experiments which will be reported in a subsequent paper suggest the disconcerting possibility that an antigen may become non-specifically enmeshed in the saline precipitate of rheumatoid arthritis serum during centrifugation, thereby increasing the intensity of the precipitate, *even though the serum contains no homologous antibodies.* It is obvious that the existence of this possibility would make it difficult ever to be certain that such a serum actually contained precipitins specific for *any* antigen. Less frequently, the reverse situation has been encountered, in which the presence of an antigen has obstructed the tendency to precipitate in saline. The enhancement of precipitation by an apparently heterologous antigen is best seen after centrifugation, but this effect may often

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be detected in the delicate particles which are present before centrifuging. Omission of centrifugation will therefore not prevent its occurrence.

To overcome the tendency of arthritis serum to precipitate spontaneously with saline, we have tried the following measures, without success: substitution of 1.7 and 3.4% sodium chloride for 0.85 and swinging the undiluted serum in an angle centrifuge before setting up the test. Samples of serum were also diluted with 3 parts of physiologic salt solution, placed in a water bath at 37° C. for 2 hours, refrigerated for 7 days and cleared in an angle centrifuge. When these sera were used in a precipitin test, no precipitate occurred in the saline control tubes, but the potency of precipitins presumed to be originally present was greatly impaired.

Agglutination of Collodion Particles. During an investigation of streptococcus precipitins in the serum of rheumatoid arthritis we undertook to convert a precipitin reaction into an agglutination by sensitizing a particulate vehicle with the antigen. Suspensions of fine collodion particles were prepared by the method of Cannon and Marshall[1] and it was found that rheumatoid arthritis sera possessing strong hemolytic streptococcus agglutinins were apt to agglutinate the particles even when they had not been sensitized by exposure to an antigen. The "collodion titers" of the arthritis sera varied rather widely with different batches of collodion particles. They ranged up to 1:2560 and could not be consistently correlated with the streptococcus agglutinin titers of the same sera. Most of the normal sera examined did not give this reaction at any strength. None was positive beyond the lowest final serum dilution used, which was 1:20. The collodion-agglutinating factor in arthritis serum is rendered inert by exposure to 65° C. for 30 minutes. Ammonium sulfate fractionation shows that it resides in the serum globulin. The agglutination of collodion particles by rheumatoid arthritis serum is apparently a non-specific flocculation analogous to the Takata-Ara, colloidal gold, cephalin-cholesterol and formol gel reactions. It is not recommended as a diagnostic test because of wide variation in the reactivity of successive batches of particles and because it is sometimes consistently negative against sera from patients with well-established rheumatoid arthritis of many years duration. Its relation to the titer of hemolytic streptococcus agglutinins will be discussed in a subsequent paper.

The tendencies of rheumatoid arthritis serum to precipitate in saline and to agglutinate suspensions of collodion particles are probably interrelated. Both are also presumably related to the globulin content of this serum, which is known[3,5] to be high.

Summary. The sera of many patients with well-established rheumatoid (atrophic) arthritis have a tendency to precipitate in the saline control tube of a precipitin test, especially after centrifugation. Many rheumatoid arthritis sera also differ from the normal in being able to agglutinate suspensions of fine collodion particles.

Conclusion. Supposedly specific reactions in which rheumatoid arthritis serum takes part should be interpreted with caution.

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REFERENCES

1. Cannon, P. R., and Marshall, C. E.: J. Immunol., **38**, 365, 1940.
2. Chasis, H., and McEwen, C.: J. Immunol., **31**, 439, 1936.
3. Davis, J. S., Jr.: J. Lab. and Clin. Med., **21**, 478, 1936.
4. Dawson, M. H., Olmstead, M., and Jost, E. L.: J. Immunol., **27**, 355, 1934.
5. Scull, C. W., Bach, T. F., and Pemberton, R.: Ann. Int. Med., **12**, 1463, 1939.
6. Wallis, A. D.: Am. J. Med. Sci., **212**, 713, 1946.

RHEUMATOID ARTHRITIS

III. The Pneumococcus Antibodies*

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As an adjunct to their study of hemolytic streptococcus agglutination by the sera of patients with rheumatoid (atrophic) arthritis, Dawson, Olmstead and Boots[3,4] have investigated the agglutinability of other gram-positive cocci by the same sera. Agglutination to a significant titer did not occur with *Strep. viridans*, *Strep. anhemolyticus*, *Staph. albus* or encapsulated pneumococci of Types 1, 2 or 3. However, non-encapsulated pneumococci derived from any of these types were agglutinated almost as strongly as the hemolytic streptococci. It is the purpose of the present paper to provide an explanation for the existence of agglutinins for the non-encapsulated pneumococcus in the serum of rheumatoid arthritis.

Materials. *Bacteria and Culture Media.* The non-encapsulated pneumococcus strain I/192/R was used throughout. Stock cultures were kept in tubes in the refrigerator in a few cc. of neopeptone broth[2] (extract of 1 pound of top of the round, grossly fat-free; neopeptone [Difco], 10 gm.; sodium phosphate dibasic, 4 gm.; tap water to make 1000 cc.; final pH 7.6 to 7.8) with the addition of a few drops of defibrinated horse blood. The same medium was used in preparing suspensions for agglutination. Unless the stock was subcultured at least once a month it lost its agglutinability. Mrs. Miriam Olmstead Lipman kindly furnished samples of the microörganism on several occasions. Cultures for extractions were grown in a tryptone glucose yeast extract broth[14] (tryptone peptone [Bacto], 20 gm.; glucose [cerelose], 5 gm.; NaCl, 5 gm.; yeast extract [Bacto], 2 gm.; dipotassium phosphate, 2.5 gm.; distilled water, 1000 cc.; final pH, 7.5). The pneumococci tended to die out after 2 or 3 subcultures unless blood was again added.

Pneumococcus C Substance.[16] For quantitative serologic use the polysaccharide was prepared by an approximation of the method of Goebel, Shedlovsky, Lavin and Adams,[8] omitting the removal of protein with copper sulfate. The acetone-precipitated polysaccharide resisted drying by suction and was dried from the frozen state by Mr. Joseph Smolens, to whom our thanks are due. About 12 mg. of a fluffy white substance were obtained from 1 liter of broth culture. For qualitative serologic use a simpler method based on the hot formamide extraction procedure of Fuller[6] yields a satisfactory product. Freshly sedimented organisms were resuspended in formamide (Eastman No. 565), 1 cc. per 100 cc. of original culture medium, and heated in a mineral oil bath at 150° to 155° C. for 15 minutes. This treatment rendered the fluid nearly transparent, indicating efficient bacterial disintegration. After cooling, the pH was adjusted to approximately 4.5, whereupon a light flocculent cloud appeared. This was spun down and discarded. It presumably included the F polysaccharide of Goebel, Shedlovsky, Lavin and Adams.[8] This is the C substance conjugated with a fatty acid. If its removal was omitted a second peak appeared in precipitin tests, attributable either to the action of anti-C in a different optimal range or to anti-F (*cf.* Goebel and Adams[7]). To the supernatant were added sodium acetate (about 10 mg. per cc.) and 3 volumes of 95% ethyl alcohol. After overnight refrigeration the copious precipitate was collected in the centrifuge and taken up in physiologic salt solution, to 2% of the original broth volume. This extract was neutralized and a large undissolved residue was discarded by centrifugation. "Mer-

* Aided by grants from the Charlotte Drake Cardeza Foundation of the Jefferson Medical College and the National Foundation for Infantile Paralysis, Inc.

thiolate" (sodium ethyl mercuri thiosalicylate, Lilly) in final concentration 1:10,000 was added as preservative.

Rheumatoid Arthritis Sera. These were from patients with typical[17] rheumatoid arthritis. They were obtained in the dispensaries and wards of the Hospital of the University of Pennsylvania, Temple University Hospital and the Philadelphia General Hospital. Preservative was added as in the case of the C substance. The tendency of such sera to precipitate spontaneously in the saline control tube of a precipitin test has been described elsewhere.[18]

Sera From Patients Without Rheumatoid Arthritis. These were obtained on the surgical and medical wards of the Hospital of the University of Pennsylvania. The patients had a wide variety of diagnoses; none complained of arthritis; all were afebrile. Their age range was comparable to that of the arthritics. Preservative was added as in the arthritis sera.

Methods. *Precipitation Tests.* The samples of arthritis serum were allowed to age in the refrigerator about 1 week, and the non-arthritis sera at least that long, before setting them up in precipitin tests. A few sera had enough opalescence to render the precipitates illegible. The tubes used were 10 x 75 mm. The antigen was used in amounts ranging downward from 0.4 cc., the volumes being made up to 0.4 cc. with physiologic salt solution, and to each tube was added 0.1 cc. of serum. With each test was included as negative control 0.4 cc. of saline without antigen. The tube contents were mixed by tapping and the tubes were incubated in a water bath at 37° C. for 2 hours. After overnight refrigeration readings were made with the aid of a reading glass (2 inch diameter, 4 inch focus, magnification 2×) held about 2 inches from the tube, a fluorescent lamp, a dark background and a darkened room. The tubes were tapped several times to make the precipitate rise and become evenly distributed. Too vigorous tapping was avoided as tending to break up the larger aggregates. Centrifugation of the tests was omitted because it aggravates the tendency of arthritis serum to precipitate in the control tube. Subsequent readings were made at daily intervals for 1 week, the tubes being refrigerated between readings. Aside from covering the tube rack with an unsterilized paper towel, no special precautions were taken to secure sterility. Visible bacterial contamination was not encountered.

Agglutination Tests. The procedure of Goebel and Adams[7] was used, with these exceptions: the bacterial suspension was diluted to approximate Tube 4 of the McFarland[13] turbidity scale; the amounts of suspension and serum dilution used were both 0.3 cc. The last tube in which agglutination was visible with a reading glass was taken as the titer. This was usually 1 tube higher than the last one in which agglutination was visible with the unaided eye. Substitution of triple for single washing of the organism had no effect on the titer.

EXPERIMENTAL. Our concept evolved in the following manner: Arthritis sera possessing hemolytic streptococcus agglutinins in high titer were set up against suspensions of non-encapsulated pneumococci, which they agglutinated in titers as high as 1:640. A few sera from normal persons, included as controls, agglutinated the pneumococci in titers of zero, 1:20 or 1:40, values comparable to Group A hemolytic streptococcus agglutinin titers of patients without rheumatoid arthritis.[3] As will appear later, these controls were not representative, but at the time we thought arthritis sera contained significant pneumococcus agglutinins. We then sought the pneumococcus component against which the arthritis antibodies were directed. The negative results of Dawson, Olmstead and Boots with encapsulated organisms indicated that this was a somatic fraction. An obvious candidate was the pneumococcus C substance,[16] which indeed proved precipitable by the serum of rheumatoid arthritis.

At this point we learned of the observation of Heidelberger and Anderson[9] (subsequently amplified[10]), that the sera of most normal persons contain measurable amounts of precipitin for the pneumococcus C substance. To determine if the precipitates with rheumatoid arthritis sera were explicable on this basis, sera from patients without rheumatoid arthritis were set up in the same manner. Com-

parison of the precipitation by sera from non-arthritic patients (Table 1, A) with that by sera from patients with rheumatoid arthritis (Table 1, B) shows that the results with the 2 kinds of serum are about the same, except that arthritis serum has a greater tendency to precipitate in the saline control and that its precipitation with the antigen is heavier when the saline control is positive. When allowance is made for this factor, arthritis serum has no more than the normal quota of anti-C. these agglutinins would *appear* to be stronger in the serum of a person who had acquired rheumatoid arthritis. Agglutinin titers are included in Table 1. Those of arthritis sera average about 2 tubes higher than those of non-arthritis sera, confirming our suspicion that the pneumococcus antibodies in arthritis serum are actually within normal limits but that their action is enhanced by the presence of a non-specific property related to the arthritis.

TABLE 1.—PRECIPITATION OF PNEUMOCOCCUS C SUBSTANCE

A. *By Representative Non-arthritis Sera*

Antigen gamma	Cha *160	Vec 160	McN 80	Hop 80	Mor 40	Kau 40	Sel 0
0 5	?fthhhh	oooo?vv	offh ± ± ±	?? ?vvvv	ooovfff	ooooooo	o?vffft
0 2	ooooovvf	ooooooo	o?vt h t t	vvvfftt	ooooovvv	ooooooo	o?vvvff
0 05	ooooooo	ooooooo	ooo? v v v	?vvvvvv	ooooo?v	ooooooo	oo?oo?v
0	ooooooo	ooooooo	oooo o o o	??oo?vv	ooooooo	ooooooo	ooooooo

B. *By Representative Rheumatoid Arthritis Sera*

Antigen gamma	Les *640	Gre 320	Lak 160	Kep 80	Far 40	Bat 40	Bro 20
0 5	f t h ± − − −	fth ± − − −	o?vtt tt	fh + + − − −	ovfttff	ooooooo	oooo??v
0 1	fh ± + − − −	?vf h − − −	ooovf ff	vf t h − − −	ovftttt	ooooooo	oooovvf
0 05	ft ± ± − − −	?vf t − − −	ooovf ff	vvf f − − −	ovffff	ooooooo	oooo?vf
0	vff t − − −	o?vv − − −	ooooooo	vvf f − − −	ovffff	ooooooo	ooooooo?

2×10^{-5} and 2×10^{-6} dilutions of antigen were used in setting up the tests. All antigen amounts were made up to 4 cc. with physiologic salt solution. Each tube received 0.1 cc. of serum. Incubation in water bath at 37° C. for 2 hours. The first reading was made after overnight refrigeration. Subsequent readings at daily intervals, the tubes being refrigerated between readings. They were not centrifuged.

The 7 columns of symbols recorded for each serum represent readings made on the first through 7th days after setting up the test. The following is the interpretation of the symbols:

Visible only with reading glass:
0 = negative
? = doubtful
v = very faint trace
f = faint trace
t = trace
h = heavy trace

Without reading glass:
± = weakest visible
+ = next stronger
− = reading not made

* The figure beneath the designation of each serum donor represents the titer of agglutinins in that serum for non-encapsulated pneumococcus. Thus, 160 signifies that a final serum dilution of 1:160 was the highest (of serial double dilutions) capable of causing agglutination.

The serum of patients with typical rheumatoid arthritis thus appears to have the ability to enhance serologic aggregations. The non-specific nature of this enhancement is emphasized by the observation[18] that such sera can agglutinate suspensions of fine collodion particles which have not been sensitized by the addition of an antigen. The implication with regard to the agglutination of non-encapsulated pneumococci by rheumatoid arthritis serum is obvious: if most normal sera contain agglutinins for this organism,

Discussion. What portion, if any, of these agglutinins is actually anti-C is a question which has no bearing on our present argument. Presumably the anti-C in normal human serum is due to the frequent presence of pneumococcus in the normal throat. This makes it likely that normal sera, and hence arthritis sera, contain antibodies against somatic pneumococcus fractions other than C. Agglutinins directed against other fractions may account for the lack of a closer correlation

between agglutinin titers and strengths of C precipitins in Table 1.

The long period of observation of precipitates in these experiments is necessitated by the inherent feebleness of human anticarbohydrate antibodies in a precipitin reaction, as compared with those of some other species, notably the rabbit. Another example is the weakness of human antisera in precipitating homologous type-specific carbohydrates of pneumococcus, as Finland and Sutliff,[5] Stats and Bullowa[15] and others have pointed out. These species differences have been attributed by Horsfall and Goodner[11,12] to qualitative differences in the phospholipid requirements of the respective antibodies when united with antigen. It is worthy of note that Heidelberger and Anderson[9] allowed human anticarbohydrate precipitates to stand 8 days in the refrigerator before collecting them for quantitative analysis.

In recording our results, designations of various degrees of "trace" for precipitates visible only with a reading glass, in addition to the more conventional plusses for grosser precipitates, have been used for the sake of emphasizing several facts, namely, that these precipitates are more delicate than those obtained with rabbit antisera, that special aids (reading glass, fluorescent lamp, dark background, darkened room) are necessary for their evaluation, and that gradations observed under these circumstances are genuine. When dealing with slight gradations, in the absence of a permanent standard for comparison, it is to be expected that a given precipitate might not always receive the same rating. In practice, the range of such variation in reading is small. For example, a "trace" might on another occasion be called a "faint trace" or a "heavy trace;" but this discrepancy does not exceed 1 gradation. The significant feature, however, is that on simultaneous comparison of a series of tubes, the relative intensities of the precipitates are easily determined. The reliability of the method is further demonstrated by examining a set of tubes on succeeding days, without knowledge of previous readings. The heaviest precipitate is found in the same tube as before, with comparable increases in all tubes.

The pneumococcus phase referred to herein as non-encapsulated is widely known as "rough." In the more logical later terminology of Dawson[1] it would be "smooth," but this classification has not received the sanction of usage.

Summary. With special visual aids and prolonged observation as substitutes for centrifugation, rheumatoid arthritis sera are found to precipitate the somatic C carbohydrate of pneumococcus a little more strongly than do sera from non-arthritic patients. The greater ability of arthritis sera in this regard is apparently related to their greater tendency to precipitate in the saline control tube of a precipitin test.

Rheumatoid arthritis sera likewise agglutinates non-encapsulated pneumococci a little more strongly than do sera from non-arthritis patients. This difference is presumably related to the ability of arthritis sera to agglutinate collodion particles.

Conclusion. The increased ability of the serum of patients with rheumatoid (atrophic) arthritis to agglutinate non-encapsulated pneumococci appears to be due to a non-specific enhancement of the action of normally present antibodies.

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REFERENCES

1. Dawson, M. H.: J. Path. and Bact., **39**, 323, 1934.
2. Dawson, M. H., and Lipman, M. O.: Unpublished.

3. Dawson, M. H., Olmstead, M., and Boots, R. H.: J. Immunol , **23**, 187, 1932.
4. Dawson, M. H., Olmstead, M., and Boots, R. H.: J. Immunol., **23**, 205, 1932.
5. Finland, M., and Sutliff, W. D.: J. Exp. Med., **54**, 637, 1931.
6. Fuller, A. T.: Brit. J. Exp. Path., **19**, 130, 1938.
7. Goebel, W. F., and Adams, M. H.: J. Exp. Med., **77**, 435, 1943.
8. Goebel, W. F., Shedlovsky, T., Lavin, G. I., and Adams, M. H.: J. Biol. Chem., **148**, 1, 1943.
9. Heidelberger, M., and Anderson, D. G.: J. Clin. Invest., **23**, 607, 1944.
10. Heidelberger, M., MacLeod, C. M., Kaiser, S. J., and Robinson, B.: J. Exp. Med., **83**, 303, 1946.
11. Horsfall, F. L., Jr., and Goodner, K.: J. Exp. Med., **62**, 485, 1935.
12. Horsfall, F. L., Jr., and Goodner, K.: J. Immunol., **31**, 135, 1936.
13. McFarland, J.: J. Am. Med. Assn., **49**, 1176, 1907.
14. Morton, H. E., and Engley, F. B., Jr.: J. Bact., **49**, 245, 1945.
15. Stats, D., and Bullowa, J. G. M.: J. Immunol., **44**, 41, 1942.
16. Tillett, W. S., and Francis, T., Jr.: J. Exp. Med., **52**, 561, 1930.
17. Wallis, A. D.: Am. J. Med. Sc., **212**, 713, 1946.
18. Wallis, A. D.: Am. J. Med. Sc., **212**, 718, 1946.

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UNDER THE CHARGE OF
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CHANGING CONCEPTS IN MEDITERRANEAN (COOLEY'S) ANEMIA

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TERMINOLOGY. In 1889, von Jaksch[79] described an anemia accompanied by splenomegaly and leucocytosis which he thought was of specific nature and to which he gave the name "Anæmia infantum pseudoleucæmica." This was subsequently called "Jaksch-Hayem-Luzet's"[7] anemia after the names of the authors who described it more fully. Later writers included under the name of von Jaksch's anemia a miscellaneous group of unrelated anemias and splenomegalies.

There appeared in 1921, in the clinic of Thomas Cooley, a brother and sister with anemia, splenomegaly, and distinctive skull changes associated with a mongoloid appearance. Other similar patients were noted over the next few years. In 1925 the series was described to the American Pediatric Society by Cooley and Lee.[22a] Not until 2 years later did Cooley and his associates[21a,23] assert that his 7 cases plus 5 others reported by Stillman and Pool[70] belonged to a definite clinical entity, a hemolytic dysfunction distinct from hemolytic icterus and sickle cell anemia, to be differentiated from other kinds of cases of the von Jaksch's type. The concept of von Jaksch's anemia promptly began to fade from prominence.

Debré and his associates[28] claim that Hayem described the condition in 1898 calling the disease "splenomegalic icterus," and that Minkowski described it again in 1900. Perusal of Debré's report makes it evident, however, that no clear line was drawn between what are now known to be 2 distinct entities, namely, Mediterranean anemia and congenital hemolytic (spherocytic) jaundice. Most writers credit Cooley as the true discoverer of the disease, for it was he who first challenged the specificity of von Jaksch's anemia and reclaimed a genuine clinical entity from the confused mass of disorders grouped under that term.

Cooley proposed the name "erythroblastic anemia"[21b] because of the large numbers of immature red cells in the peripheral blood. Later developments have shown that this term was not the best,[43] as Cooley himself later realized, for it causes confusion between this specific entity and other anemias characterized by erythroblastosis such as "erythroblastosis fœtalis" due to the Rh factor. The term erythroblastic anemia has become further unsuitable with the uncovering of the "carrier" state and of mild clinical and subclinical forms in which

nucleated red blood cells may be absent. In truth, anemia itself is not an essential diagnostic criterion.

Because of the predilection of the disease for children of Greek, Italian, Syrian or Armenian parents, Whipple and Bradford[83b] suggested "Thalassemia" or "Mediterranean anemia" from the Greek word for "great sea." Cooley, feeling the use of his own name for the designation of the disease added another undesirable eponym, adopted the term Mediterranean anemia for his own clinic.[21d]

The severe and readily recognizable form originally described by Cooley has assured the anemia its place in the standard pediatric texts. However, more recent investigations[68b,c,86] are showing that the disease has a wide range of clinical severity and that mild cases may have no anemia and normal life spans. Mediterranean anemia has thus spread from the bounds of pediatrics to invade the realm of adult medicine. This has further complicated terminology. Mediterranean "disease" would seem more accurate than "anemia." Smith[68b] uses the terms "severe" and "mild" for the gradations of severity. Valentine and Neel[75a] propose "thalassemia minor" and "thalassemia major" for the corresponding conditions. Under "target-oval cell syndrome" Damashek[26c] includes the entire range of variation from the frank advanced case to the patient who presents naught but minimal hematologic abnormalities.

The Carrier State. Some years ago, Angelini[4] and Caminopetros[15a] proposed the existence of a genetic carrier, as evidenced by blood studies, results of the fragility test, and mild roentgenographic changes. Caffey[14a] also had hypothesized that mild cases can reach adult life and transmit the disease.

Wintrobe's[85] confirmation of Angelini's and Caminopetros' observation that the parents of active cases had decreased fragility of the red blood cells supplied the final link. This related to Mediterranean anemia various other anemia syndromes such as Damashek's[26a] "Familial Mediterranean Target-oval Cell Syndrome," Strauss and Daland's[72] "Familial Microcytic Anemia," the "Microcytic Hypochromic Anemia Associated With Splenomegaly and Refractory to Treatment" of Eliel and Bayles,[32] "La Syndrome di Cooley nell'Adulto" described by Chini,[17] the "Familial Hemopoietic Disorder in Italian Adolescents and Adults" reported by Wintrobe and associates,[86] and the observations by Goldhamer[37] of characteristic blood changes in several members of 1 family over a span of 3 generations.

Etiology. The etiology is obscure. Cooley, Witwer and Lee[23] originally believed that the disorder was not primarily hemolytic but rather a disorder of hematopoiesis due to a metabolic fault which also affected bone maturation. Because none of the early reported cases survive puberty, they felt that heredity played no part. Whipple and Bradford[83b] offered the possibility of an inherited metabolic disorder or a deficiency disease which resulted in disturbed erythropoiesis, faulty bone formation, and bodily development. They compared the lack of a vital factor to that found in pernicious anemia. Lehndorff[47] suggested that the primary disturbance lay in a disturbed bone marrow, which because of some hereditary or "mutational" influence was creating defective red cells.

Impressed with the great similarity of the blood findings in Mediterranean disease and chronic malaria, Nittis and Spiliopulos[58] suggested that Mediterranean anemia may be a peculiar form of malaria. Eight children ranging in age from 1 to 12 years were treated with quinine. In 2, malarial parasites were found before treatment had been started. Within 3 months after treatment, all had improved clinically and hematologically.

Similar reports from Greece and Italy have stressed the importance of malaria as an etiologic factor, either directly on the child or indirectly through injury of the germ-plasm or fetus in the mother before or during pregnancy.[5,18,39] Flynn[35]

cautions us to remember that malaria is very common in Greece and Italy. The possibility of coincidental infection would be difficult to exclude. Caminopetros[15a,b] was of the opinion that a coincidental malarial infection in Mediterranean anemia was effective in relieving many of the symptoms.

Smith[68c] found no history of malaria in the individual members of the 16 families whom he studied. All but 1 of the children and 9 of the affected parents were born in the United States. Fawdry,[34] on the basis of his studies on Greeks on Cyprus, concluded that malaria played no part in the causation of the disease, although a few observers in the Mediterranean countries, such as Aravantinos,[5] prefer to believe that this is an "infectious or parasitic process" with an affinity for the hemopoietic system. No relationship to the Rh factors has been demonstrated.

Damashek[26b] has suggested, because of the hypochromia, the low mean corpuscular volume, and the failure of response to iron medication, that a disturbance exists in the metabolism of hemoglobin, particularly in development of a normal amount in the cytoplasm of the nucleated red blood cells of the bone marrow. The hyperplasia of the marrow, normoblastic in type, is so extensive in proportion to the evident blood destruction that some cause, other than the constant one arising from the demand to replace the cells lost by fragmentation, is to be sought. Cooley[21d] postulated either a primary progressive abnormality of the bone marrow or a hyperplasia due to long-continued overstimulation. The presence of large numbers of circulating erythroblasts in some cases has led to the obvious suggestion that these immature cells have escaped into the circulation as the result of chronic demand on a particular type of hyperplastic inadequate bone marrow or because a lowered threshold for the release of erythroblasts occurs as part of the disorder.

The fundamental defect lies obviously in the production of red blood cells. In the advanced cases the variation in size and shape of the cells is extensive; hypochromia is prominent; the cells contain so little pigment that their destruction yields little jaundice of the serum; and polychromatophilia and reticulocytosis can be demonstrated. The presence of large numbers of stippled cells suggests the possible action of some toxin, but this seems unlikely in view of the hereditary nature of the process.[26b] More likely the stippling is a manifestation of a defect in structure of the corpuscle.[68c]

Erythrocytes in every stage of development may be seen. Commonly found are macrocytes with unusual central and peripheral deposits of hemoglobin, the so-called "target cells." (See later discussion of this cell.)

Damashek[26b] offered as possible cause for the increased hemolysis seen in severe cases: (1) Increased breakdown of hemoglobin precursors which cannot be properly metabolized. (2) A possible increased *in vivo* fragility of the target cells although *in vitro* it has increased resistance to hypotonic salt solution. (3) Some abnormality in the spleen.[9]

Similarly Wintrobe and his associates[86] suggested that the fundamental defect lay in the production of abnormal red blood cells possessing an adequate or excessive membrane with but little cytoplasmic substance. As a result, the cells withstand the hemolyzing effect of hypotonic solutions more readily than normal cells. Much more fluid needs to be absorbed from a hypotonic solution to produce the spherical shape which is preliminary to bursting. Bradford and Dye[11] studied the morphology of the red cells in 8 cases. Wet preparations revealed marked fragmentation. "Knob-like projections were observed to form and to break off from the erythrocytes with regularity." In 2 children, after splenectomy, the cells showed a normal or decreased mean corpuscular volume and an increased mean cell diameter, which suggested cells thinner than normal. Price-Jones distribution curves usually show wide bases and in-

creased coefficients of variations in comparison with normal blood.

Cooley[21d] believed that the fragmentation and the peculiar, irregular deposits of hemoglobin in the cells are related. The abnormal physico-chemical structure of the cells predisposes them to rapid breakdown in the circulation. This would account for the anisocytosis and poikilocytosis so often observed. The many microcytes seen in the moist film are in part produced by fission of large cells. Valentine and Neel,[75a] on the basis of their exhaustive original studies and analysis of the recorded cases, have concluded, and apparently rightly, that Mediterranean anemia is due, not to lack of extrinsic iron, but to an inherited inability of the body to utilize or synthesize some substance essential to normal erythropoiesis. "Thus far, efforts to identify the missing factor in thalassemia have been entirely unsuccessful." According to this concept, the difference between the mild and severe forms would be a matter of difference in the capacity to elaborate the unknown deficient substance.

The enlargement of the spleen which appears early is probably due to its overactivity in disposing of the products of fragmentation.[21d] The spleen shows no evidence of increased erythrophagocytosis. The enlargement of the liver is probably associated with persistent anemia; Whipple and Bradford[83b] discovered that the liver at postmortem contains about 10 times the amount of iron normally found, whereas the spleen holds less than the normal amount.

After splenectomy, there is a marked rise in the number of nucleated red cells in the peripheral blood. A level of 2200 per 100 white blood cells may be reached.[21b,71,83a,84] Unlike the transient normoblastic crisis which follows splenectomy in hemolytic icterus and pernicious anemia, the level of nucleated red blood cells continue permanently at an elevated level. It is difficult to explain this, unless the possibility is entertained that the spleen has previously been actively destroying these cells.

Whipple and Bradford[83b] pointed out the peculiar pigment distribution in the tissues that could be duplicated in only one other condition, hemochromatosis. The pigments which are chiefly iron-staining are increased throughout the tissues, except in the spleen which contains less than the usual amount of iron. Since the patterns of pigment distribution are almost identical for both hemochromatosis and Mediterranean anemia, these authors concluded that the blood disturbance alone is probably not responsible for the pigment abnormalities in Mediterranean anemia.

Valentine and Neel[75b] attempt to explain the disturbance in terms of an inherited inability of the body to metabolize completely more than a limited amount of iron into hemoglobin, regardless of the quantity of iron ingested or stored in the body reserves. Thus there would be a deficiency of some factor essential for hemoglobin synthesis, the deficiency being quantitatively much greater in the fatal form of the disease than in the milder genetically related variety. The iron-containing pigments found in the viscera could be explained as being some pigment precursor of hemoglobin which, incapable of being synthesized further, becomes deposited in tissues much as in ochronosis; incompletely metabolized products of tyrosine become deposited in cartilage. Carrying this explanation further, the erythroblastosis becomes the result of the extreme degree of iron deficiency; the bone changes are a response to the markedly hyperplastic bone marrow; and the jaundice, never marked, becomes due to the tendency for all abnormally shaped red cells to be destroyed more rapidly than normal red cells, regardless of the nature of the abnormality.

Target Cells. Haden and Evans[41] in 1937 described in fresh preparations of blood of patients with sickle cell anemia red cells which had "a central 'sugar loaf' elevation so that in profile they had the appearance of a Mexican hat instead

of a dumbbell." On stained smear these cells had a peripheral ring and a central dot of hemoglobin with a pale or unstained intermediate zone. The unusual morphology was deemed to be in some way related to the abnormal tendency to hemolysis or the ease of fragmentation. The cells were believed to have an unusual capacity for taking up water so that they almost doubled their volume before hemolysis resulted.

The following year, Barrett[8] showed that these cells occurred in obstructive jaundice even when the hemoglobin and red counts were normal, after splenectomy, in steatorrhea, and in a group of anemias in which the color index was not more than 0.8. Similar cells were later noted in Laennec's cirrhosis, catarrhal jaundice, metastatic involvement of the liver and cardiac decompensation.[56]

Noting that when viewed from above at different levels these cells presented a "bull's eye" appearance, Barrett[8] suggested the name "target cell," which was quickly accepted. He showed that the increased resistance to hypotonic solutions associated with the presence of target cells was due not only to the increased resistance of the target cells themselves, but to the tendency of these cells to be associated with other cells of a resistant type. His measurements revealed the target cell to be of slightly smaller diameter (7.662 μ) than the normal cell (8.045 μ). He questioned Haden and Evans' description of the cell as "dimpled," and proposed "umbonate" instead, because of the central projections. Studies on wet films revealed that target cells exist in the blood as bowl-shaped precursors. Only on drying does the characteristic "target" appear. In the process of drying bowl-shaped cells form a hump in the center.

Barrett felt, as had Haden and Evans, that the increased resistance of this type of red cell was probably related to the morphology. A decrease in thickness appeared to be the most constant characteristic. He compared the target cell to a bladder which is collapsed and almost empty. As fluid passes into it, it becomes gradually more distended, but not until the spherical stage is reached will there be any significant increase in the tension of the cell envelope.[16] According to Haden's theory[40,77] which is essentially a mechanical one, the thicker the cell the greater the fragility and *vice versa*. The precursor of the target cell, the bowl-shaped cell has a surface-volume ratio of relatively high magnitude. In its transformation to the target corpuscle the cell envelope is thrown into folds so that it is larger than that of the disc-shaped corpuscle. This makes for a cell envelope which has a surface relatively large compared to the cell volume.

In 1938 target cells were identified by Bywaters[13] in a case of Mediterranean anemia. Although not commented on in the text, target cells are evident also in the blood films illustrating Caminopetros' paper (1938)[15a] on Mediterranean anemia. Since then their presence in this disease has become well recognized. The increased resistance (decreased fragility) was confirmed by Damashek[26a] and later by Bohrod.[10a,b] However, in direct contrast to Barrett, Damashek found in his cases that the target cells were larger than the average red cell; he also noted their frequent presence in Mediterranean anemia. Bohrod[10a,b] believed the target cell to be a young hyperresistant one produced by the bone marrow in response to blood loss, regardless of cause. He found them present in most chronic anemias, and regarded their occurrence as analogous to that of the reticulocyte. Damashek[26a] regarded the target cell as a congenitally defective cell, probably the fundamental defect in Mediterranean anemia. He pointed out that a cell which is hyperresistant to the *in vitro* hypotonic solution test may nevertheless be hyporesistant to the *in vivo* destructive mechanisms. Cooley[21c] in his Presidential address before the American Pediatric Society commented likewise that these cells bear no specific relationship to Mediterranean anemia.

Recent evidence indicates that lyso-

lecithin in the relatively stagnant blood of the spleen may increase erythrocyte fragility. Ham and Castle's[42] studies indicate that the spleen is the chief stasis organ of the body and that as a result of first physical, and later metabolic changes, the red blood cells become spheroidal and more fragile. Kniseley[46a,b] showed in the living animal that blood free of plasma stagnates in the splenic sinusoids for several minutes to several hours. All these studies tend to confirm the opinion that the red blood cells become modified in their passage through the spleen in the direction of increased sphericity and increased hypotonic fragility.

On the basis of the foregoing and Barrett's establishment of a morphologic background (the target cell) for the increased hypotonic resistance of the red blood cells after splenectomy, Singer and his associates[67] postulate the possibility of a hyposplenic condition in Mediterranean anemia. They noted the appearance of target cells in the blood following splenectomy in dogs and guinea pigs, and ligation of the splenic veins in dogs. They conceive that the erythrocytes when first produced in the bone marrow are relatively thin, but later develop a "normal" degree of thickness on passing through the sinusoids of the spleen. Accordingly, when the spleen is absent, the red cell population tends to be thinner than normal and a definite proportion of red blood cells become sufficiently thin to be recognized as target cells. The possibility is also advanced that the spleen may exert some hormonal influence on the late stages of maturation of the erythrocyte. In the absence of such a hypothetical factor, target cells may develop.

Smith[68c] is similarly convinced that the target cell is non-specific and that decreased fragility does not depend on their presence. Of 53 individuals examined who had a mild form of Mediterranean anemia plus increased resistance to hypotonic solutions, only one-half showed target cells in their blood. Microscopic examination of the sediment in the tubes in the extremely dilute solutions of sodium chloride often failed to reveal the bowl-shaped precursors of the target cell.

Valentine and Neel[75a,b] disagree with Vohrod's contention that the target cell is only a young hyperresistant form appearing in the blood as a response to blood loss. They have repeatedly seen evidences of the bone marrow pouring out large numbers of young cells in the absence of target cells. They disagree with Damashek's view that the target cell is the fundamental inherited defect in Mediterranean anemia. They deem the target cell to be a thin, resistant cell, of non-specific nature. They point out that this cell is encountered in many other conditions, that some patients with undoubted Mediterranean anemia fail to display it, and that the number of such cells which appear in a stained blood smear depends to some extent upon the manner of preparation of that smear. They had been able to produce target cells *in vitro* by suspending normal red cells in plasma or serum rendered hypotonic either by the addition of chemicals or by evaporation.

Diagnostic Criteria. The severe form usually has its onset in early infancy, as early as the 3rd or 4th month, though its presence may not be suspected until the 5th or 6th year of age. The first apparent symptom is usually pallor. Anorexia and fatigue are also noted early. A protruding abdomen or palpable spleen may be the first finding to invite further examination.

The anemia is constantly progressive and before many months the disease process becomes well established. Malnutrition and retardation of growth are present in varying degrees. The characteristic facies usually does not become apparent until after the 1st year and sometimes not until several years. The mongoloid appearance results from development of the malar and orbital bones. This causes some prominence and slanting of the eyes. The appearance is heightened by the subicteric tinge of the skin. The prominence of the upper teeth are a result of protrusion due to hyperplasia of the maxilla.[20,59]

The abdomen becomes progressively protuberant with increase in size of the liver, and especially the spleen. The spleen may become so weighty that the small child cannot stand up without support lest he be thrown forward. Lymphadenopathy is slight. The scleræ may become mildly icteric. The urine may be dark from urobilin but almost never contains bile. There are no characteristic hemolytic crises but exacerbations may occur during infection.

True cardiac hypertrophy has been demonstrated repeatedly.[13,57] Hemic murmurs are readily audible and in advanced cases cardiac action may eventually become embarrassed. In the late stages, ecchymosis and free bleeding may be seen. Pathologic fractures are not uncommon. Corcoran[24] described an 8 year old boy who first came to medical attention because of a spontaneous fracture of the left femur.

Of more recent interest is the recognition of mild or asymptomatic forms of the disturbance. The mild or "minor" form is beginning to be recognized as widely prevalent, in contrast to the marked or "major" form which is more familiar but comparatively uncommon. (See a later section of this Review for a summary of surveys regarding prevalence.) Careful study of the blood may be the only means by which the mild form may be detected. Subtle roentgenologic bony changes may also be demonstrable.

Well-established cases have anemia as a prominent symptom, but the mild form may have a normal or even increased red cell count.[26b,86] In both varieties the hemoglobin content is usually lower than the red cell level, giving rise to a low color index. In Smith's[68c] studies on 54 affected parents and siblings, in 16 families, morphologic changes in the red cells were detected in all individuals regardless of the intensity of the anemia. Smith's description is representative of the current understanding of the red cell abnormalities. "These changes consisted of varying degrees of hypochromic anemia, occasionally polycythemia, an elevated icteric index, the presence of target cells, reticulocytes, macrocytes and stippled red cells, and increased resistance of the red cells to hemolysis. The most common findings, regardless of the severity of the anemia, were anisocytosis and poikilocytosis, basophilic stippling and increased resistance to hypotonic sodium chloride solution. The hypochromic and polychromatophilic macrocytes constituted an important diagnostic feature and were frequently found in predominantly microcytic blood smears." He found a reticulocyte increase ranging from 2 to 8% in all subjects with anemia, the increase being proportional to the severity of the anemia. The number of stippled cells was not always proportional to the number of reticulocytes. Nucleated red cells free in the blood stream were found only with advanced anemia. The vast majority of nucleated red blood cells were normoblasts.

Diversity of red cell size was another prominent feature in Smith's cases. There was a tendency to microcytosis with large cells interspersed. In mild cases the macrocytes were few in number, but in anemic cases they often appeared in great numbers. Smith[68c] described 3 types of macrocytes. The first is the target cell which is seen in about half of patients with the mild form of the disease. The second is a circular or slightly oval cell having a narrow rim of hemoglobin and a large central achromic area. The third cell, and the one Smith believes to be the most specific, is large and pale and bears its hemoglobin irregularly distributed. This cell looks as if defectively stained. It is extremely thin and leaflike and in wet preparations the edges fold over.

The majority of his mild cases showed a normal or slightly decreased volume of packed red blood cells accompanying the slight to moderate reduction in hemoglobin content. Regardless of severity, anisocytosis and poikilocytosis were invariably present. Smith found, as had Wintrobe[86] previously, that morphologic changes were far out of proportion to the

mildness of the anemia. Polychromatophilia, Howell-Jolly bodies, Cabot rings, nuclei and reticulated markings appeared frequently.

The fragility test is believed by Smith to be the most important single procedure for recognition of both the mild and the advanced forms. In Mediterranean anemia the span of fragility of the red blood cell is prolonged. In Mild cases unhemolyzed cells may be found in 0.175% solutions of sodium chloride. In severe cases, hemolysis may not be complete until distilled water is used. Angelini[4] first called attention to the importance of the fragility test in detecting the mild case or carrier. This was confirmed independently by Caminopetros.[15]

In the advanced disturbance the leucocytes are usually moderately elevated. One of the patients of Whipple and Bradford[83a] had a count of 116,000. The leucocytes are usually immature types such as early myelocytes and young lymphocytes.[53] Platelets may be normal or reduced. The bleeding and coagulation times are usually within normal limits. The van den Bergh test, if positive, is indirect and the icteric index may be as high as 20. Urine and feces usually show increased amounts of urobilinogen. The serum, calcium, phosphorus and lipids fall within normal limits. In the mild cases no disturbance in the hemopoietic system is usually elicitable apart from morphologic and resistance changes in the red cells.

Resistance to antianemic therapy aids in the diagnosis. When an infant or young child of Mediterranean origin free from infection fails to respond to adequate iron therapy, his future course will probably be that of Mediterranean anemia.[68c]

Almost always 1 or both parents or grandparents come from one of the Mediterranean countries. The tendency to familial occurrence is of extreme importance in diagnosis. Clinical findings are usually marked only when the anemia is well established and progressive.

Whipple and Bradford[83b] emphasized the pigment abnormalities in advanced cases which follow accurately the pattern of pigment distribution in hemochromatosis. Deposition of iron-containing pigments in the skin cause the characteristic subicteric tint.[52]

The bone marrow shows marked hyperplasia. Parent stem cells of the marrow (hemocytoblasts) are abundant. Myelocytes of all types are numerous as are megakaryocytes. Normoblasts are present in great excess; megaloblasts not so abundantly.[30,34,78]

Highly characteristic is the increased outpouring of immature red cells which follows and persists after splenectomy. As already mentioned, all observers agree that splenectomy is productive of no clinical improvement apart from the mechanical relief gained by removal of a large and heavy organ from the persistently distended abdomen. The red blood cell count and hemoglobin level appear to remain unchanged after splenectomy.

Little can be added to the observations of Caffey[14a,b] on the skeletal changes. These findings are essentially non-specific and characteristic of all the chronic hemolytic anemias of infancy and childhood though it is in severe Mediterranean anemia that they are most marked and most frequent. Identical lesions have been seen in chronic malaria, kala-azar and syphilis.[35] All observers are agreed that the changes in the bones are not primary but secondary to increased blood formation, taking place before the cortex is sufficiently firm to resist the expanding marrow. The extent of skeletal change is usually parallel to the severity of the anemia. Mild anemias have but little bone changes. The later in childhood the disease becomes manifest, the less marked is the osteoporosis.

In the skull, overgrowth of hemopoietic tissue widens the diploic spaces by displacing the outer table externally. The frontal bone becomes the site of the earliest and later of the most marked thickening. The radiating spicules of the frontal and parietal bones may make these bones 5 times their normal thickness.[12] Swell-

ing of the zygoma cheek bones contributes to the mongoloid appearance. The internal expansion of the swollen upper maxilla sometimes obliterates the maxillary sinuses. Skull thickening may antedate the long bone changes, or *vice versa*.

The long and short tubular bones are uniformly involved, with widened medullary canals, thinned cortices and general osteoporosis. Heavy trabeculations, particularly near the ends of the shaft, may cross irregularly through the medullary spaces. During late childhood and early adult life sclerosis may supervene. Maturation and growth of the skeleton may be retarded. The bone changes come after the blood changes. They have been observed as early as age $4\frac{1}{2}$ months,[14a] though most of the marked cases have had apparently normal bony contours until after ages 6 to 9 months. Splenectomy appears neither to accelerate nor retard the development of bone lesions.

Genetic Behavior. There is little doubt that Mediterranean anemia has a hereditary origin, even though the severe cases usually fail to reach adolescence, and those who have gone on to maturity have failed to procreate.[50] The question is not whether it is transmitted, but how?

Angelini[4] supplied early evidence for a hereditary origin. In a study of 26 members of 6 families, he found that nearly all the parents and siblings showed two striking features—a slight bilirubinemia and an increase in the resistance of the red blood cells to hemolysis. The absence of sex linkage is well established although Rundles and Falls[64] have described a somewhat similar form of anemia thus transmitted.

Caminopetros,[15a] working at the Pasteur Institute of Athens, found 35 cases of Mediterranean anemia in eastern Greece and made detailed observations on several generations of 4 families, 1 for 4 generations. He demonstrated mild bone changes in apparently healthy members of the family as well as an increased resistance to hypotonic solutions of sodium chloride. He postulated on the basis of his studies that the disease is transmitted according to the Mendelian law as a recessive character. His study of the family trees brought out the surprising fact that the ancestry of these Greeks included some Chinese who had migrated to Asia Minor. This might account for the "Mongolian eye" occasionally found in some cases.

McIntosh and Wood[50] concluded that failure to discover a significant excess of marriages of cousins among the cases over that present in the community at large argued against the mechanism of simple recessive inheritance, although the theoretic ratio of 1 affected to 3 unaffected siblings was demonstrated. These authors state that dominant inheritance "may operate to produce Mediterranean anemia in the children of apparently healthy parents in 1 of at least 3 ways: first, by recent mutation of genes as in amaurotic family idiocy; second, by operation of some as yet unrecognized environmental factor which allows the genetic trait to be expressed; third, by association of 2 genes, each of them rare and each capable of producing a recognizable deviation from normal when occurring alone in the parents, but causing an anemic syndrome only when found simultaneously in 1 person." They discount the first 2 hypotheses on the basis that these fail to account for the 1:3 ratio of affected to unaffected siblings, and for the occurrence of the anomaly in twins, and conclude that 2 dominant genes is the most plausible method of transmission. They suggest that the increased resistance of the red cells may be the expression of 1 of these synergistic genes.

Cooley[22b] believed the inheritance was by a simple dominant. He rejected the idea that the disease was race-limited. "When a disease-producing mutation takes place, it recurs first in the neighborhood of its origin. It is limited to a race in proportion to the clannishness and isolation of the people involved. The appearance in a Negro or Chinese child must not be attributed to an unlikely racial

cross. Such occurrences may be explained on the new appearance of mutations which set up new foci of the disease."

Damashek's[26b] studies on 10 Italian families with target-oval cell syndromes led him to believe that the mild disorder was readily transmitted by a Mendelian dominant, but that the severe disorder required the presence of homozygous genes.

Smith[68b,c] found in every family he studied with a severely affected child that both parents presented abnormalities of the blood, except in 1 family incompletely investigated. Smith suggests that inheritance is by a dominant gene, judging by the family pedigrees of his cases and those of others.[56,75a,86]

Valentine and Neel[75a] have made a thoughtful analysis of the manner of inheritance, basing their considerations upon a review of the literature and observations of 34 persons in 4 affected families. In these families 24 persons had hematologic findings qualitatively similar but quantitatively less severe than those of full-blown Mediterranean anemia (which the authors prefer to call thalassemia), including increased resistance of erythrocytes to hypotonic solutions of sodium chloride, target and oval red blood cells, microcytosis, and hypochromia. Valentine and Neel scrutinize the 3 most likely patterns of inheritance. The first is that the severe form results from homozygosity for a factor which when heterozygous produces the mild anemia, *i. e.*, the responsible factor is either an incomplete recessive or a semidominant. Otherwise stated, the full-blown disease is inherited as a recessive characteristic, but the heterozygote as well shows significant changes in the blood. This is the theory of Caminopetros[15] and Dameshek.[26] The second likely pattern of inheritance is that proposed by Cooley[21c] and Smith[68c] that both the severe and the mild conditions have the same genetic basis and are due to a dominant factor variably expressed. Thus 1 person heterozygous for this factor may have a severe disturbance, and another one only minor changes, the different reactions being determined by environmental and genetic modifiers. The third likely pattern is that suggested by McIntosh and Wood[50] who proposed that the disease is caused by the simultaneous presence of 2 non-allelomorphic dominant factors, 1 inherited from each parent. After discussing these alternative possibilities Valentine and Neel conclude, from considerations too lengthy to reproduce here, that "the bulk of evidence, with one significant departure, favors the hypothesis that the mild state is due to heterozygosity for a factor which when homozygous results in full-blown thalassemia." The authors present this view as the working approach which fits the known facts best, even though certain trends remain puzzling, such as the tendency for a significant excess of mildly affected individuals among the offspring of mildly anemic and normal parents. Technically they favor the theory of an incomplete recessive gene, although Gates[36a] from a review of the same series of cases inclines toward the view that the gene is a partial dominant, sublethal when homozygous.

Prevalence and Distribution. The disease is largely confined to the population living along the Mediterranean littoral and their descendants. Many writers confine the disease to the northern shore, but it has been reported from both shores.[30] Most of the patients come from Greece, Sicily, and Calabria. Strangely enough, the first case from Italy was not reported until 1934,[62] almost 10 years after Cooley's original description. Many believe that the southern Italians with the disease are partly of Greek origin.[27] During the height of the Greek era of civilization and particularly during the reign of Alexander the Great, there was extensive colonization of all the Mediterranean countries by Greece, with subsequent intermarriage. Fawdry[34] found many advanced cases among the Greek inhabitants of Cyprus; in $2\frac{1}{2}$ years as medical officer in 1 district he encountered 20 such patients, 19 children and 1 adult.

Investigation of the fossilized bones of the mound builders of eastern Arkansas,[81] and of the pre-Columbian Peruvians[6] indicate that in those past civilizations a disease existed whose roentgenologic findings are identical with Mediterranean anemia.[87]

A number of instances of an identical or closely similar anemia have been reported in non-Mediterranean races. Saracoglu[65] described Mediterranean anemia in a 9 year old Turkish boy whose brother had died from a severe anemia. This is the fourth reported case among individuals of Turkish descent. Sendrail *et al.*[66] observed a Spanish case. Bywaters[13] described a 10 year old ill child with a blue-eyed English policeman as father, an English mother, and 4 healthy siblings.

Diwani[30] found the disease in 2 Egyptian children. Mukherji[54] has recorded a 30 month old Hindu male with this anemia. Patel and Bhende[60] noted a Brahmin boy who had the disease complicated by cirrhosis of the liver and kyphosis. Coelho[19] has observed 2 Indian girls aged 6 and 9 years, and Napier[55] and his associates a Hindu boy aged 10 years. Dhayagude[29] has described a 7 year old Brahmin boy who had the disease in a moderately severe form, and from New Delhi, Malhotra and Chhuttani[49] have reported a 4 year old affected child.

The first case in a Chinese child was reported in 1940 by Foster.[36] No Roentgen rays were taken of the skull or long bones. The mother had hematologic findings suggestive of a mild form of the disease. Wang and Khoo[82] in the same year report 3 cases of hemolytic anemia with erythroblastosis in Chinese children. One of the 3 appeared to have Mediterranean anemia.

Damashek[26b] in his article on the "Target Cell Syndrome" (1943) mentions a typical case of Mediterranean anemia in a Negro child observed at the Mt. Sinai Hospital of New York. Stiles, Marlowe and Dangerfield[69] describe a 33 year old Negro with the hematologic findings of the disease; this individual's mother and sister also had histories of anemia and a maternal great-grandparent was of Italian origin. Faber and Roth[33] report an instance in a Negro girl. Damashek,[26c] who has often seen target and oval cells in Negroes with no evidence of sickling, states the entire subject needs amplification. Downey[31] feels that many cases in other races may have been overlooked because the symptoms are sought only among Mediterranean descendants.

Neel and Valentine[56] made a city-wide survey of the number of individuals of Italian descent living in Rochester, N. Y. and the prevalence of Mediterranean anemia among them. These individuals for the most part were immigrants or descendants of immigrants from Sicily or southern Italy. Survey of hospital records revealed the occurrence of the severe form of the anemia was 1 per 2368. From this datum they estimated the number of mild cases which might be present among this same population, basing their calculation upon the hypothesis that severe Mediterranean anemia is an inherited disorder due to homozygosity for an inherited factor, whereas the milder disorder is due to heterozygosity for the same factor. Their calculation led to the ratio 1 per 25 adult Italians for the frequency of the minor disorder in Rochester's population. This estimate has thus far not been validated by direct study of representative samplings.

Prognosis. The prognosis is contingent on the fact that the disease shows a wide range of variation, from the "trait" or carrier state to the advanced form marked by severe anemia. Individuals having the mild form may and usually do have a normal span of life, whereas individuals having the severe form, with onset early in life, marked anemia, splenomegaly, and bony changes, rarely survive adolescence. They succumb from profound anemia or intercurrent infection. Very occasionally, a temporary remission may be induced by transfusion or splenectomy. Less often a more or less permanent

remission takes place at blood levels compatible with moderate normal activity.

The number of reports keeps growing of patients with moderately severe anemia and marked hematologic abnormalities with or without clinical and roentgenologic findings who have survived adolescence. Mandeville[48] described a 15 year old with an advanced roentgenologic picture. No mention is made of any associated findings. In 1936, a 24 year old Italian pharmacist with pallor, jaundice and splenomegaly who had a normoblastic crisis after splenectomy was reported by Allen and Childs.[2] Dalla Volta's[25] patient, aged 30, showed considerable excess pigment in his organs and large cells suggesting the foam cells described by Whipple and Bradford.[83a] Caminopetros[15a] listed 2 adults with Mediterranean anemia and Aravantinos[5] 3 aged 16, 21 and 22 years. Thalheimer[74] reported a 14 year old male whose illness dated from 1 year of age, and added a note regarding a 16 year old patient mentioned to him by Dr. Benjamin Kramer of the Jewish Hospital of Brooklyn. Atkinson[6] followed 2 adult siblings of Greek parentage, a brother and sister, 17 and 20 years old, with characteristic findings, for a period of 12 years. A Sicilian youth of 20 with splenomegaly and a hypochromic microcytic anemia resistant to therapy was seen by Wintrobe;[86] since the age of 10 this patient had presented a degree of hypochromia and poikilocytosis out of all proportion to the anemia. Eliel and Bayles[32] described a 39 year old American born Italian woman who had a hypochromic, microcytic anemia with splenomegaly, subclinical jaundice, and blood change characteristic of the Mediterranean anemia of childhood. Fawdry[34] reported an adult Greek male on Cyprus, 20 years old, who had stunted growth, cardiac enlargement and a mongoloid facies. Smith's[68b] 19 year old boy was first described in 1942. He had been followed since the age of 4 and was last transfused in 1929. A younger brother, aged 8, also with Mediterranean anemia, is being treated symptomatically without transfusion. Van Ravenswaay's[76] patient who practised forms of treatment quite primitive was 35 years old. The 20 year old male described by Voorhies and Sloan[80] demonstrated a characteristic hematologic picture, mongoloid facies and extensive bony changes. Read's 36 year old male apparently had a mild form of Mediterranean anemia.

Of course, now that the great reservoir of mild cases has been discovered, distinction must be made between the mild and severe, or "minor" and "major" forms of the disorder when adult patients are being discussed.

TREATMENT. There is very little that has been left untried in the treatment of Mediterranean anemia. Feeding of various liver and splenic fractions have given negative results. Adrenal cortical extract has been tried without success. Anterior lobe of the pituitary, thymus and bone marrow extracts failed to modify the clinical picture. Vitamin concentrates, raw pancreas, predigested beef, and pentanucleotide have proven of little avail.[83b] No specific corrective or prophylactic treatment is known. All therapy must be directed toward preventing complications and offering symptomatic relief. This anemia is almost the only exception to the dictum that a hypochromic anemia always responds to iron therapy.[36b]

Hunter,[41] in an attempt to depress the hemopoietic organs so that escape of immature nucleated erythrocytes into the blood stream might be prevented, gave Roentgen ray in dosages in excess of the optimal. Acute bone marrow depression was produced. Aided by transfusions, the platelets and white blood cells returned to normal levels. After several weeks, the red cell count rose to a higher level than had been observed at any time prior to the irradiation. The clinical condition also showed improvement. No reports of further follow-up studies were published. Wang and Khoo[82] tried Roentgen ray therapy with 1 of their patients. There was a marked depression of all blood elements including the platelets. Daily irra-

diation of the spleen of a 9 month old patient by Amesse and Barber[3] offered no relief and was discontinued when the patient became worse.

Nittis and Spiliopulos,[58] noting a similarity in the blood findings in Mediterranean anemia and chronic malaria, attempted intensive antimalarial therapy in 8 patients having the advanced picture of Mediterranean anemia. Seven of the 8 showed clinical and hematologic improvement 3 months after therapy. In direct contrast, Caminopetros,[15a] observing the benefit which occurred in a thalassemic patient who developed a coincidental malarial infection, inoculated 7 other patients with the disease. His results led him to state that this therapy was as effective as is Roentgen ray therapy in leukemia.

Goldman and Malavazos,[38] taking into account Whipple and Bradford's opinion that the basis of the pathologic process lay in a vitamin or endocrine disturbance, tried pregnancy urine and vitamin B_6 with 3 patients. All responded with bone marrow hyperplasia of the erythrogenic series, and moderate increase in the red cell count in the peripheral blood; but as treatment was continued beyond 4 weeks a fall in the count took place.

Van Ravenswaay *et al.*[76] described a primitive treatment practised by a 35 year old patient in his youth in a small town in Greece. (This patient had 3 children who died of Mediterranean anemia.) Four to 6 folds of skin would be lifted over the liver or spleen and each fold would be nicked with a knife. Then a tumbler was held over this area with a lighted piece of cotton placed inside. This consumed the oxygen and created a suction. The tumblers were left in place until they loosened themselves which was usually when one-third full of blood. As many as 4 to 5 tumblers would be used at one time. Native children have also been taught to lean over a sharp piece of furniture such as a table and compress the spleen for as long as they could stand the pain. Improvements in breathing would follow, and the patients would repeat this procedure 6 to 8 times per day.

Splenectomy is of no great value.[1,2,4,73,84] It is practised only in patients with marked weightiness of the organ or mechanical obstruction. Very occasionally a temporary remission will follow splenectomy.

Blood transfusions are without permanent benefit.[61] Nevertheless, periodic transfusions should be given to maintain blood levels compatible with normal activity. Koteen and Brooks[45] have set up an out-patient transfusion clinic for patients with this disorder. Adequate levels of hemoglobin and red cells are maintained by whole blood transfusions every 2 weeks. Transfusion maintains the hemoglobin and erythrocytes on low but constant levels. When the levels begin to drop more transfusions are required. Transfusion reactions though frequent are usually not serious. Only with the aid of repeated transfusions have children with severe Mediterranean anemia lived to and beyond adolescence. The 19 year old thalassemic described by Smith[68b] is an exception. Valentine and Neel[75a] caution against using blood for these patients drawn from the parents or relatives because: "1. Frequently the donor's blood is significantly hypochromic, so that the hemoglobin content per 100 cc. of blood is below the desired optimum. 2. More important, erythrocytes which have the same type of defect inherent in the erythrocytes of the recipient, albeit quantitatively less severe, are being transfused. There is presumptive evidence that such cells are undergoing more rapid destruction than normal erythrocytes, in the body of both the carrier, who is the donor, and the thalassemic recipient. 3. It is undesirable to bleed donors whose hemopoietic apparatus is already overstrained and defective. It seems likely that the supportive value of such transfusions may be significantly reduced. Transfusion from an extraneous normal donor or from a proved normal relative is a more rational procedure."

Conclusions. The observations summarized in the preceding pages represent

a body of information impressively elaborate when one considers that the disease Mediterranean anemia was not recognized as an entity until 2 decades ago. Numerous problems related to it are as poorly understood now as when Cooley and Lee made their first report. The basic defect has an inherited origin, and probably is more closely related to red cell than to hemoglobin formation (though both seem defective in advanced cases), but what is its precise nature? The recognition of the carrier state represents a major step forward, of as great importance to adult as to pediatric medicine, yet the mechanism of genetic transmission has become more rather than less obscure as a consequence of this discovery. Valentine and Neel's estimate of 1 affected carrier per 25 individuals of Italian origin clamors for corroboration. We must have adequate knowledge regarding heredity in order to be able to give eugenic advice to young couples when 1 or both are found to carry the trait. Treatment, of course, has always been highly unsatisfactory, palliative transfusion being the only helpful procedure known. Widespread attention should be given to Koteen and Brooks' experience in an out-patient transfusion clinic. If transfusions can be given to active cases in out-patient departments at frequent regular intervals, the rate of infections will decrease, the costs to hospitals will diminish and the children themselves will fare better.

REFERENCES

(1.) **Acuna, M.**: Arch. argent. de pediat., **16**, 126, 1941. (2.) **Allen, E. G.**, and **Childs, D. S.**: New York State J. Med., **36**, 641, 1936. (3.) **Amesse, J. W.**, and **Barber, W. W.**: Colorado Med., **34**, 241, 1937. (4.) **Angelini, V.**: Minerva Med., **2**, 331, 1937. (5.) **Aravantinos, A.**, and **Delijannis, G.**: Klin. Wchnschr., **15**, 1792, 1936. (6.) **Atkinson, D. W.**: Am. J. Med. Sci., **198**, 376, 1939. (7.) **Atkinson, F. R. B.**: Brit. J. Child. Dis., **37**, 89, 1940.

(8.) **Barrett, A. M.**: J. Path. and Bact., **46**, 603, 1938. (9.) **Bergenhem, B.**, and **Fahræus, R.**: Ztschr. f. d. ges. exp. Med., **97**, 555, 1936. (10.) **Bohrod, M. G.**: (*a*) Am. J. Med. Sci., **202**, 869, 1941; (*b*) J. Lab. and Clin. Med., **26**, 1953, 1941. (11.) **Bradford, W. L.**, and **Dye, J.**: J. Pediat., **9**, 312, 1936. (12.) **Bush, G. B.**: Brit. J. Radiol., **10**, 491, 1937. (13.) **Bywaters, E. C. L.**: Arch. Dis. Child., **13**, 173, 1938.

(14.) **Caffey, J.**: (*a*) Am. J. Roentgenol., **37**, 293, 1937; (*b*) Pediatric *X*-ray Diagnosis, Chicago, Year Book Publ., p. 727 ff., 1945. (15.) **Caminopetros, J.**: (*a*) Ann. de méd., **43**, 27, 1938; (*b*) Ibid., **43**, 104, 1938. (16.) **Castle, W. B.**, and **Daland, C. A.**: Arch. Int. Med., **60**, 949, 1937. (17.) **Chini, V.**: Rassegna Clin. Scient., **17**, 435, 481, 1939. (18.) **Choremis, K.**, and **Spiliopulos, G.**: Jahrb. f. Kinderh., **148**, 317, 1937. (19.) **Coelho, G.**: Med. Bull., Bombay, **7**, 291, 1939. (20.) **Cohen, M. M.**, and **Baty, J. M.**: J. Am. Dent. Assn., **32**, 1396, 1945. (21.) **Cooley, T. B.**: (*a*) Am. J. Dis. Child., **33**, 786, 1927; (*b*) Ibid., **36**, 1257, 1928; (*c*) Ibid., **62**, 1, 1941; (*d*) Brennemann-McQuarrie System of Pediatrics, Hagerstown, Md., Prior, **3**, Chap. 16, 56, 1945. (22.) **Cooley, T. B.**, and **Lee, P.**: (*a*) Trans. Am. Ped. Soc., 1925, *in* Am. J. Dis. Child., **30**, 447, 1925; (*b*) Ibid., **43**, 705, 1932. (23.) **Cooley, T. B.**, **Witwer, E. R.**, and **Lee, P.**: Am. J. Dis. Child., **34**, 347, 1927. (24.) **Corcoran, W. J.**: Radiology, **43**, 373, 1944.

(25.) **Dalla Volta, A.**: Arch. di pat. e clin. med., **15**, 34, 1935. (26.) **Damashék, W.**: (*a*) Am. J. Med. Sci., **200**, 445, 1940; (*b*) Ibid., **205**, 643, 1943; (*c*) New England J. Med., **234**, 829, 1946. (27.) **Davison, C.**, and **Wechsler, I. S.**: Am. J. Dis. Child., **58**, 362, 1939. (28.) **Debré, R.**, **Lamy, M.**, **See, G.**, and **Schrameck, G.**: Am. J. Dis. Child., **56**, 1189, 1938. (29.) **Dhayagude, R. G.**: Am. J. Dis. Child., **67**, 290, 1944. (30.) **Diwani, M.**: Arch. Dis. Childhood, **19**, 163, 1944. (31.) **Downey, H.**: Handbook of Hematology, New York, Hoeber, vol. **3**, 1938.

(32.) **Eliel, L. P.**, and **Bayles, T. B.**: New England J. Med., **225**, 134, 1941.

(33.) **Faber, H. K.**, and **Roth, B. M.**: J. Pediat., **28**, 610, 1946. (34.) **Fawdry, A. L.**: Lancet, **1**, 171, 1944. (35.) **Flynn, J. M.**: Brit. J. Radiol., **16**, 157, 1943. (36.) **Foster, L. P.**: Am. J. Dis. Child., **59**, 828, 1940.

(36*a*.) **Gates, R. R.**: Human Genetics, New York, Macmillan, vol. **1**, 1946. (37.) **Goldhamer, M. L.**: Ohio State Med. J., **38**, 321, 1942. (38.) **Goldman, L. M.**, and **Malavazos, A.**: J. Clin. Endocrinol., **1**, 945, 1941. (39.) **Grillo, C.**: Pediatria, **48**, 791, 1939.

(40.) **Haden, R. L.**: Am. J. Med. Sci., **188**, 441, 1934. (41.) **Haden, R. L.**, and **Evans, F. D.**: Arch. Int. Med., **60**, 133, 1934. (42.) **Ham, T. H.**, and **Castle, W. B.**: Proc. Am. Philos. Soc., **82**, 411, 1940. (43.) **Holt, E.**, and **McIntosh, R.**: Holt's Diseases of Infancy and Childhood, 11th ed., New York, Appleton-Century, p. 188, 1940. (44.) **Hunter, F. T.**: New England J. Med., **214**, 1123, 1936.

(45.) **Koteen, P.**, and **Brooks, N.**: J. Pediat., **28**, 697, 1946. (46.) **Knisly, M. H.**: (*a*) Anat. Rec., **65**, 23, 1936; (*b*) Ibid., **65**, 131, 1936.

(47.) **Lehndorff, H.**: Ergebn. d. inn. Med. u. Kinderh., **50**, 568, 1936.

(48.) **Mandeville, F. B.**: Radiology, **15**, 72, 1930. (49.) **Malhotra, R. P.**, and **Chhuttani, P. N.**: Indian Med. Gaz., **79**, 198, 1944. (50.) **McIntosh, R.**, and **Wood, C. L.**: Am. J. Dis. Child., **64**, 192,

1942. (51.) **Miller, E. B., Singer, K.,** and **Damashek, W.**: Proc. Soc. Exp. Biol. and Med., **49**, 42, 1942. (52.) **Mills, E. S.**: Arch. Int. Med., **62**, 1004, 1938. (53.) Mitchell-Nelson Textbook of Pediatrics, Philadelphia, Saunders, p. 873, 1945. (54.) **Mukherji, M.**: Indian J. Pediat., **5**, 1, 1938.

(55.) **Napier, L. E., Shorten, J. A.,** and **Das Gupta, C. R.**: Indian Med. Gaz., **74**, 660, 1939. (56.) **Neel, J. V.,** and **Valentine, W. N.**: Am. J. Med. Sci., **209**, 568, 1945. (57.) **Nemet, G.,** and **Gross, H.**: Am. Heart J., **12**, 352, 1936. (58.) **Nittis, S.,** and **Spiliopulos, G.**: Am. J. Dis. Child., **54**, 60, 1937. (59.) **Novak, A. J.**: Am. J. Orthodont. and Oral Surg., **30**, 539, 1944.

(60.) **Patel, N. D.,** and **Bhende, Y. M.**: Indian J. Pediat., **6**, 217, 1939. (61.) **Pierce, M. L.**: Am. J. Dis. Child., **61**, 654, 1941.

(62.) **Ravenna, F.,** and **Canella, C.**: Policlinico, **41**, 807, 1934. (63.) **Read, J. J.**: Ohio State Med. J., **41**, 623, 1945. (64.) **Rundles, R. W.,** and **Falls, H. F.**: Am. J. Med. Sci., **211**, 641, 1946.

(65.) **Saracoglu, K.**: Wien. med. Wchnschr., **93**, 217, 1943. (66.) **Sendrail, M., Lyon, A.,** and **Lasserre, J.**: Bull. et mém. Soc. méd. d. hôp. de Paris, **52**, 902, 1936. (67.) **Singer, K., Miller, E.,** and **Damashek, W.**: Am. J. Med. Sci., **202**, 171, 1941. (68.) **Smith, C. H.**: (*a*) J. Pediat., **16**, 375, 1940; (*b*) Ibid., **20**, 370, 1942; (*c*) Am. J. Dis. Child., **65**, 681, 1943. (69.) **Stiles, M. N., Marlowe, C. M.,** and **Dangerfield, C. D.**: Northwest. Med., **45**, 23, 1946. (70.) **Stillman, R. G.,** and **Pool, E. H.**: The Surgery of the Spleen, New York, Appleton, 1923. (71.) **Stransky, E.,** and **Regala, A. C.**: Am. J. Dis. Child., **63**, 859, 1942. (72.) **Strauss, M. B., Daland, G. A.,** and **Fox, H. J.**: Am. J. Med. Sci., **201**, 30, 1941. (73.) **Styron, C. W.**: South. Med. and Surg., **101**, 316, 1939.

(74.) **Thalheimer, E. J., Mezzetti, A.,** and **Gershon-Cohen, J.**: J. Pediat., **14**, 349, 1939.

(75.) **Valentine, W. H.,** and **Neel, J. V.**: (*a*) Arch. Int. Med., **74**, 185, 1941; (*b*) Am. J. Med. Sci., **209**, 741, 1945. (76.) **Van Ravenswaay, A. C., Schnepp, K. H.,** and **Moore, C. V.**: J. Am. Med. Assn., **122**, 83, 1943. (77.) **Vaughan, J. M.**: J. Path. and Bact., **45**, 561, 1937. (78.) **Vogel, P.,** and **Bassen, F. A.**: Am. J. Dis. Child., **57**, 245, 1939. (79.) **von Jaksch, R.**: Wien. klin. Wchnschr., **2**, 435, 1889. (80.) **Voorhies, N. W.,** and **Sloan, F. R.**: J. Am. Med. Assn., **125**, 352, 1944.

(81.) **Wakefield, N. D., Dellinger, S. C.,** and **Camp, M. D.**: Am. J. Med. Sci., **193**, 488, 1937. (82.) **Wang, C. Y.,** and **Khoo, F. Y.**: Chinese Med. J., **58**, 177, 1940. (83.) **Whipple, G. H.,** and **Bradford, W. L.**: (*a*) Am. J. Dis. Child., **44**, 336, 1932; (*b*) J. Pediat., **9**, 279, 1936. (84.) **Williamson, C. R.,** and **Crawford, R.**: New Orleans Med. and Surg. J., **98**, 280, 1945. (85.) **Wintrobe, M. M.**: Clinical Hematology, Phila., Lea & Febiger, 1942. (86.) **Wintrobe, M. M., Matthews, E., Pollack, R.,** and **Dobyns, B. M.**: J. Am. Med. Assn., **114**, 1530, 1940. (87.) **Wood, B. J.**: Proc. Staff Meet., Mayo Clinic, **16**, 202, 1941.

GYNECOLOGY AND OBSTETRICS

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OVARIAN TUMORS

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Tumors originating in the ovary continue to be of great interest to the clinician as well as the gynecologic pathologist, judging by the great number of papers which have been published in recent years. To the clinician, once the diagnosis of an ovarian tumor has been made, the chief interest lies in knowing whether or not it is malignant. To the pathologist, however, the details of structure, origin and classification carry the study into much finer ramifications. For those who are interested in this highly specialized field of gynecologic pathology, the recent collective review of Dockerty[6] will be of great value. While the review which is here presented will overlap Dockerty's at some points, it will stress the clinical rather than the pathologic aspect.

Granulosa Cell Tumor. This tumor, which produces estrogenic hormone, is being more frequently recognized each year. In a study of 21 cases Henderson[11] found that they presented considerable variation in gross and microscopic appearance. The smallest tumor was microscopic in size while the largest weighed 24 pounds. The moderate sized tumors, as a rule, revealed areas of interstitial hemorrhage, cystic degeneration and necrosis. The solid portions were whitish in color and of brainlike consistency. Marked friability was a constant feature of those tumors which were predominantly of the follicular type. The common clinical evidence of hormone activity was uterine bleeding alternating with irregular periods of amenorrhea. Amenorrhea of 3 to 4 months duration was common while periods as long as 2 years were occasionally observed. When such long periods of amenorrhea occurred during the age period of the menopause it was often difficult to determine whether the amenorrhea was due to a physiologic menopause or to the tumor. Endometrial hyperplasia of the "Swiss-cheese" type was the common pathologic evidence of excessive estrogen secretion. During the postmenopausal years, myometrial hypertrophy frequently accompanied the endometrial hyperplasia while, in the 1 case occurring before puberty, secondary sex characteristics were precociously developed. Evidence of biologic activity of the tumor was present in 15 of the 21 cases. In 10 cases the evidence was endometrial hyperplasia and in 5 it was a clinical history of irregular uterine bleeding. There were 5 cases of uterine fibroids as well as 2 cases of carcinoma of the endometrium. Until more is known about the malignant potentialities of the granulosa cell tumor and the effect of irradiation on a large number of cases has been observed it would seem wise to advise postoperative irradiation in all cases in which the tumor occurs at the time of, or after, the menopause. Considerable variation in the rate of growth of these neoplasms was evident. One patient was observed for $3\frac{1}{2}$ years without any increase in size of the neoplasm, while the largest

tumor in the series occurred in a patient whose only complaint was a rapidly enlarging abdomen for 1 year. Another case demonstrated marked rapidity of growth following the intrauterine application of radium for metrorrhagia.

At the Mayo Clinic, according to Hodgson, Dockerty and Mussey,[12] between 1910 and 1944 there were 62 granulosa cell tumors removed. This constitutes 1.63% of 3800 ovarian tumors encountered during this period. About 60% of these tumors were found in women who had passed the menopause. The most common clinical symptoms were uterine bleeding (74% of 62 cases), amenorrhea (22%) and abdominal enlargement (29%). From a study of the records it was apparent that the tumors that produced these symptoms grew slowly and might have been present for as long as 35 years. Evidence of hyperestrinism is afforded in this series by symptoms of precocious puberty, amenorrhea and postmenopausal bleeding, and is supported by the incidence of adenomyosis and endometriosis (9.6%), which often occurred in postmenopausal patients; uterine fibromyomas 51.6%, uterine hypertrophy 59.6% and proliferative endometrium 67%. Differentiative (secretory) changes in the endometrium were correlated in 3 cases with luteinization in the granulosa cell tumor. Luteinization without the expected endometrial change was observed in 12 additional tumors. Thus the deduction that granulosa cell tumors may produce the differentiative hormone, progesterone, is suggested. The high incidence (21%) of endometrial carcinoma observed in 38 postmenopausal patients who had granulosa cell tumor was remarkable. In 3 of the 8 cases, carcinoma of the breast with axillary metastasis also developed. This phenomenon of coëxistent ovarian, endometrial and mammary carcinoma in the human being bears a marked similarity to the results of experiments on laboratory animals in which estrogen stimulation appears to be a factor in carcinogenesis. In this group of 62 cases of granulosa cell tumor there were 4 definite recurrences and 1 possible recurrence. Conservative surgical procedures among the postmenopausal patients accounted for 4 and possibly 5 failures to obtain good results. Thus 4 recurrences and 3 deaths occurred after conservative operations in the postmenopausal group. This appreciable incidence of recurrences among older patients indicated that bilateral oöphorectomy with hysterectomy is advisable for granulosa cell tumors affecting women past middle life. Less radical procedures, on the other hand, seem to be indicated for granulosa cell tumor affecting younger women, inasmuch as no recurrences were noted and pregnancy subsequently occurredin 3 cases.

In regard to the curability of granulosa cell tumors, Jones and Te Linde[14] of the Department of Gynecology at Johns Hopkins Hospital have found that as these tumors become more commonly recognized, it is apparent that the prognosis is more difficult to determine than formerly believed. It was at first thought that these tumors were benign. As the number of case reports multiplied and the follow-up studies were available, it became evident that the granulosa cell tumor, although more benign than most other ovarian carcinomas, nevertheless carried with it a definite malignancy. The difficulty in the prognosis of the granulosa cell tumor is further reflected by the wide variation of statements in the literature concerning its malignancy. The occurrence of malignancy among the granulosa cell tumors is quoted by various authors as being as low as 10% and as high as 55%, with all intermediate gradations. The collection of adequate statistics on the malignancy of the granulosa cell tumor is difficult as the incidence of late recurrence in this tumor group makes 5 or even 10 year follow-up studies inadequate. This fact has been strikingly brought to their attention by the recent return of 3 patients to the gynecologic clinic, all having recurrent granulosa cell tumors 15, 16 and 19 years, respectively, after their original operation. All 3 pa-

tients have died, 18, 20 and 21 years, respectively, following the removal of the primary tumor, in spite of the fact that the tumors were well encapsulated and showed no evidence of metastasis or implantation at the original operation. One case recurred in spite of a bilateral salpingo-oöphorectomy and a hysterectomy. One case with widespread inoperable abdominal metastases, responded well to deep Roentgen ray therapy over a period of 3 years but a subsequent recurrence of the growth proved refractory to treatment. Total urinary estrogen values were not extremely high in 2 cases but within the range of values for normal cyclic women. However, the values were well above those usually found for postmenopausal women, into which age group all 3 patients fell at the time of recurrence. All 3 cases exhibited clinical signs of estrogenic activity on recurrence of the tumor.

THECA CELL TUMORS. Although it is less than 15 years since theca cell tumors of the ovary have been accurately described, they have attracted considerable attention. In analyzing 23 of these tumors Banner and Dockerty[1] state that the tumor probably arises from certain pluripotential mesenchymal cells of the ovarian cortex and is related on the one hand to the histologically mature fibroma and on the other to the comparatively dedifferentiated granulosa cell neoplasm. Controversy still exists, however, in regard to certain clinical, pathologic and physiologic aspects of the tumor and further statistical data are necessary to elucidate some of these issues. In their series theca cell tumor appeared to be relatively rare. It comprised about 3% of the group of solid ovarian tumors, was about a third as common as granulosa cell tumor, and was less than a tenth as common as ovarian fibroma. The average age of patients who had theca cell tumors was about 54 years; 65% of the patients were 50 years of age or older. Extremes of 80 and 26 years were noted. Theca cell tumors have not been reported as occurring prior to the age of puberty. Pregnancy had occurred at least once in 80% of the patients. Irregular vaginal bleeding of the postmenopausal type or gross menstrual irregularities of younger patients existed in more than 60% of the reviewed cases. The largest tumor measured 12 cm. in its greatest diameter and the smallest 3 mm. The average diameter was about 6 cm., the actual size of the tumor bearing no apparent direct relation to the degree of clinical "function" as measured by the duration or the severity of associated menstrual disturbances. The color of the tumors varied considerably. The outer aspect, usually smooth and often bosselated, presented tints ranging from brownish gray or even pearly to a dull orange yellow. This latter color was nearly always apparent somewhere on cut section of the tumor. The consistency was in general firm but rubbery rather than densely hard and inelastic. Degenerative central cysts were present in several of the larger tumors and these cysts appeared to arise through chronic infarction and edema as a result of twisting of the pedicle of the tumor. Residual ovarian tissue could be found in the capsules of all but the larger neoplasms. A smooth glistening capsule invested all but 2 of the tumors, and these 2 appeared to be fixed by adhesions to neighboring structures. These tumors appear to be derived from the ovarian mesenchyma and they are closely related to the granulosa cell group of tumors. Occasionally the relation may be a histologic one with elements of both types discernible within the same neoplasm. Usually, however, both tumors present "purity" of type. The relatively high incidence, especially in postmenopausal patients, of associated myometrial hypertrophy and uterine fibromyomas, combined frequently with endometrial hyperplasia and cervical and fundal carcinoma, suggests the production by the ovarian tumors of estrogenic hormone. Inability to demonstrate measurable quantities of this hormone through assays of tumor tissue is perhaps not to be regarded as conclusive evidence of absence of the

hormone. Although the tumors did not invariably produce clear-cut clinical symptoms, their presence could often be suspected by an alteration in the menstrual habits of the patient. Postmenopausal bleeding from a hypertrophic endometrium was commonly encountered in these patients.

In reporting 4 cases of theca cell tumors McGoldrick and Lapp[20] have reviewed the subject and state that not infrequently there are no menstrual abnormalities noted. Varying degrees of virilism have been reported in 3 instances. Atypical bleeding may be cyclic or irregular, scanty or profuse. Other changes noted are a rejuvenation of atrophic breast tissue, recrudescence of libido, and a revitalization of the vaginal mucosa. Physiologically, because of the hyperestrinism produced by the tumor, the uterus becomes enlarged and softened with glandular cystic or adenomatoid hyperplasia of the endometrium. All symptoms abate upon extirpation of the tumor. In the premenopausal group, the periods again recur regularly; in the postmenopausal group, the bleeding ceases. They state that the tumor is always unilateral, no bilateral theca cell tumors ever having been reported. Thecoma tends to simulate the fibroma of the ovary in size, shape and consistency. A capsule is commonly present. On cut section, the surface is noted to be composed of varying sized islands having a diagnostic yellow hue and separated by grayish white fibrous bands. Small cystic areas are an inconstant feature and result from liquefaction necrosis. At the most, theca cell tumors are a form of low grade ovarian malignancy. Most surgeons feel that treatment need not be radical, a simple excision of the ovary being sufficient in the vast majority of cases. Theca cells are considered to be radioresistant, so that radiation therapy is generally considered to be of little or no value except for the diminution of the size of the tumor by the effect of Roentgen ray on the fibrous tissue stromal elements.

ARRHENOBLASTOMA. While the granulosa cell and theca cell tumors may be called feminizing tumors because they secrete female sex hormones, the arrhenoblastoma is a masculinizing tumor and is a much rarer tumor than the others. In presenting a case of this type Kanter and Klawans[16] state that when virilism exists in the female, several conditions must be considered in differential diagnosis since adrenal and pituitary disease can both cause the condition. Cushing's syndrome, basophilic adenoma of the pituitary, is characterized by hypertrichosis and amenorrhea but no hypertrophy of the clitoris or larynx and no ovarian tumor. On the other hand, there are hypertension, glycosuria, obesity of face, neck and trunk, acrocyanosis and interference with visual fields. The adrenogenital syndrome may be quite difficult to differentiate from arrhenoblastoma since most of the symptoms of one are present in the other. The presence of an ovarian tumor would point to arrhenoblastoma but the tumor may be so small that it cannot be palpated. The adrenal may be visualized by Roentgen ray after perirenal air insufflation, but here also the tumor may be too small to be visualized. Careful blood and urine studies may give a clue to the diagnosis. Adrenal tumors are associated with hypertension, a decrease in serum sodium and in increase in serum potassium. The urinary sodium is increased to 3 times normal and the potassium in urine is decreased.

In a study of 70 cases collected from the literature, which were all the cases available up to the time of their report, Krock and Wolferman[17] have gleaned several interesting observations. The conclusions of investigators on sex reversal, that the right ovary exhibits testicular transformation more often than the left in animals, is not borne out in the human, since the tumor was found on the left side in 31 cases, and in 2 it was stated as occurring on both sides. It is also to be noted that the histologic pictures, as reported, lack the necessary degree of uniformity to be convincing that this unusual

tumor is a distinct pathologic entity. Alteration of secondary characteristics in the female is not limited to one particular group of ovarian tumors. There are many reports of masculinizing ovarian tumors in which histologic examination has failed to disclose the presence of testicular elements. In other words, we have, on one hand, the so-called "arrhenoblastoma" with a variable picture of masculinization clinically but with what apparently are testicular elements histologically, and, on the other hand, a number of different types of ovarian neoplasms in which the predominant tissue is other than testicular, but with clinical virilism. The one thing common to 2 such widely divergent pictures is the presence of tridermal tissue elements, which can be demonstrated by routine studies in approximately one-third of the cases. To create a new pathologic entity, based upon the predominant tissue present, as has been done with arrhenoblastomata, would lead to hopeless confusion. In the final analysis, our present knowledge is still deficient concerning the exact origin of all the factors controlling the development of secondary sexual characteristics. Upon this basis, it is their plea that all masculinizing ovarian tumors be classified as teratomata with a one-sided development, be such development testicular elements (either in the form of interstitial cells or seminiferous tubules), adrenal cortical remnants, or even other tissues or their anlagen whose rôles at present under normal conditions, in the development of the secondary sexual characteristics of the individual, are not fully understood. Or we may retain the term "arrhenoblastoma" to indicate such a "clinicopathologic" condition, rather than regard it as representing one constant pathologic entity to be pigeon-holed thus by any pathologist inspecting the tissue microscopically.

A most interesting and unusual case of arrhenoblastoma, complicating pregnancy, probably the first instance of its kind has been reported by Brentnall.[2] The reason for the extreme rarity of the 2 conditions in the same patient is that once a tumor has produced its first symptoms, amenorrhea, the woman is sterile but usually several months must pass before the symptoms of virilism appear. There is, therefore, only a very short period during which pregnancy and virilism can synchronize. This patient was delivered by Cesarean operation and it is of interest to note that the child was normal except for the external genital organs which were those of a pseudohermaphrodite.

The term *gynandroblastoma* was first used by Robert Meyer in 1930 in a case of arrhenoblastoma which had in part a histologic similarity to granulosa cell tumor and was accompanied by uterine hypertrophy. He suggested that ovarian tumors may arise from indifferent elements which become morphologically and functionally hermaphroditic so that they may cause both hypertrophy of the uterus and masculinization. In reporting a case of their own and after reviewing the literature, Mechler and Black[21] state that ovarian tumors exist in which there is alteration of the secondary sexual characters of the bearer in the male direction, presumably as a result of the androgenic hormone liberated by the tumor; but at the same time there is a continuation of cyclic menstrual bleeding, with indications of hyperestrinism. Such cases differ from granulosa cell tumors both biologically and histologically. There is no constant cell pattern in these cases, and they appear to represent combinations of granulosa cell tumors and arrhenoblastomas. The presence of tubular structures lined by cylindrical, mucus-secreting epithelium has been noted. Interstitial cells carrying lipoids, resembling the testicular Leydig cells, are common to both gynandroblastomas and arrhenoblastomas. There is presumptive evidence that these cells are the source of the androgenic hormone. The question of antagonism between the androgenic and estrogenic hormones in gynandroblastomas is complex. Androgenic hormones are capable of inhibiting menstruation in the normal woman, theo-

retically by inhibiting the gonadotrophic factor of the hypophysis, thereby preventing ovarian formation of estrin. This does not apply in case of the tumor, necessarily, as the tumor cells may be able to produce estrin independently of hypophyseal factors. Therefore, hyperestrinism and virilism may coëxist in the same person. The term gynandroblastoma may be usefully applied to describe a clinical-pathologic syndrome, but there is no constant accompanying histologic pattern. The ovarian tumor concerned has epithelium-lined tubules and interstitial cell groups in common with arrhenoblastoma. The impression is gained that combinations of the granulosa cell tumor with arrhenoblastoma do occur but that one element or the other usually predominates to the extent that the double biologic effect is lacking. It is suggested also that the gynandroblastomas are teratomatous.

DYSGERMINOMA. In contrast to the previous tumors which we have considered, the dysgerminoma elaborates no sex hormones and is the tumor most frequently associated with pseudohermaphrodites and women with poorly developed genitalia. In presenting a case of this type, Long, Ziskind and Storck[19] comment that while a large pelvic tumor in a pseudohermaphrodite or in a female with infantile genitalia suggests dysgerminoma, the diagnosis is not so easily made in those women who have normal secondary sex characteristics. Aside from symptoms referable to a disturbance of hormonal balance, the complaints and findings are usually those due to a large and rapidly growing pelvic tumor. Changes in the menstrual period, abdominal pain and enlargement are the common complaints. The tumor, as a rule, enlarges rapidly, attaining a size sufficient to fill the lower abdomen in 3 to 6 months. Degeneration of the fast growing mass frequently occurs and is sometimes responsible for fever, night-sweats and leukocytosis up to 20,000 cells per c.mm. Other more infrequent symptoms, some of which are due to pressure, others to malignant extension, are renal colic, urinary frequency, respiratory embarrassment, diarrhea, vomiting, ascites, anemia and loss of weight. The tumor is one of childhood and young adulthood, frequently having its onset early in puberty. In this characteristic it varies widely from its homologue, the testicular seminoma, which rarely is found before the 30th year. The diagnosis rests largely upon a consideration of the duration of symptoms, the age of the patient, state of sexual development, and the presence of a rapidly growing pelvic neoplasm. Palpation of the abdomen and pelvic examination reveal a hard, elastic mass with an irregular, nodular surface. Occasionally the Roentgen ray may be able to differentiate between a teratoma or dermoid cyst from a dysgerminoma by demonstrating the presence of calcium in the tumor. Opinions as to the incidence of malignancy in dysgerminomas vary. As yet there are such few cases on record and each writer's experience is so small that no clear conception of the degree of malignancy has been gained. The pathologist is able to add little to the problem's solution, for histologically all dysgerminomas display malignant features, and there appears to be no constant relation between these and the degree of malignancy. At present the most valuable criteria of the malignancy of individual tumors are clinical. If at operation a unilateral tumor is found which has no obvious extension, as indicated by the absence of infiltration of adjacent structures and regional lymph node involvement, it may be regarded as benign until proved otherwise by the clinical course. Infiltration of the broad ligament, uterus, opposite ovary, rectum and bladder, and lymphatic spread to the retroperitoneal lymph nodes occur in a definite proportion of cases, but metastases to distant organs are rare. The importance of accuracy in estimating the degree of clinical malignancy at the time of the operation is self-evident when the occurrence of dysgerminomas in young individuals is placed in relation to the effective methods of treatment of the malignant phase, *viz.*,

radical surgery and deep Roentgen ray therapy. The price paid by the patient for this form of treatment is removal or destruction of both ovaries. While this fate is of little concern to the pseudohermaphrodite or to the patient with marked hypogonadism, it is undesired by the young girl who has not yet developed secondary sex characteristics and by the young woman who desires to bear children. Simple extirpation has come to be considered good judgment on the part of the surgeon who finds at operation a solid, non-adherent, ovarian tumor. Should gross and histologic study prove the mass to be a dysgerminoma, frequent follow-up examinations should be made in an effort to discover early any possible recurrence of the neoplasm, which when found should then be treated by irradiation. If, on the other hand, there is present at operation evidence of local extension, a more radical surgical procedure should be adopted and followed after operation by deep Roentgen ray therapy. In inoperable cases, thorough irradiation alone remains the treatment of choice. Those patients whose advanced dysgerminomas are attacked early are offered an excellent prognosis. The cut section presents a homogeneous, friable, glistening, brainlike surface through which run scanty fibrous septa. Areas of yellowish discoloration indicate lipoid degeneration, and frequently this has progressed to the stage of frank necrosis with the formation of broad zones of necrotic tissue and hemorrhagic cysts of varying size. The microscopic appearance of sections of dysgerminoma is one of the most characteristic found among solid ovarian tumors. The tumor cells are large and round with hyperchromatic centrally placed nuclei containing large nucleoli, and a narrow lightly granular cytoplasm. Frequent mitotic figures appear. The cells are loosely arranged in column or islands, frequently described as alveolar, separated by varying amounts of loose, edematous, poorly vascularized connective tissue. Degenerative changes and hemorrhages are common. The connective tissue nearly always is diffusely infiltrated with lymphocytes, and these with the presence of small epithelioid cells and large giant cells create a picture simulating tuberculosis.

Brenner Tumor. This is another of the rare ovarian tumors which is usually unilateral. In reporting a case of bilateral Brenner tumors Johnson and Dockerty[13] remind us that the Brenner tumor comprises 2% of solid ovarian tumors, which in turn comprise only 20% of all ovarian tumors. Brenner tumors may be divided into 2 groups, namely, (1) a completely solid tumor (70%) and (2) a solid tumor in the wall of a cyst, usually a pseudomucinous cystadenoma (30%). Brenner tumors vary in size from a microscopic nodule to a huge growth almost filling the abdominal cavity. Small tumors cause no symptoms, being discovered at necropsy. The majority of Brenner tumors are found after the menopause. They never occur before the onset of puberty. In their series of 20 cases, the ages of the patient varied from 34 to 75 years. Although uterine bleeding has been present in a number of reported cases, there is no proof that this bleeding is on a hormonal basis. The most common complaint is of an abdominal tumor. In all cases reported in the literature the tumor was benign, but these growths frequently are associated with other neoplasms of the genital tract. Macroscopically, Brenner tumors resemble ovarian fibromas, being whitish in color, dense and hard. Microscopically, the picture is uniform. There are islands of squamous-like epithelial cells in a dense stroma of fibrous tissue. The peripheral rows of these cells frequently are arranged in palisades. Some of the islands are cystic with an inner lining of columnar, mucus-producing cells. Mitotic figures are not observed. These tumors are to be distinguished from granulosa cell tumor and from metastatic squamous cell epithelioma. In any solid ovarian tumor, especially of the bilateral variety, the possibility of Krukenberg's tumor should be

kept in mind and exploration of the upper part of the abdomen should be undertaken. Johnson and Dockerty state that there are 3 fairly plausible hypotheses of origin. The first is that of Robert Meyer who reported that Brenner tumors had been derived from Walthard's cell rests which frequently are found in the cortical and medullary zones of normal ovaries. These rests undergo metaplasia to form Brenner tumors. However, these rests often are found in the mesosalpinx and underneath the serosa of the fallopian tubes, locations in which Brenner tumors never are encountered. The second hypothesis is that of Schiller who noted a close resemblance between certain glands of the posterior urethra and the epithelial elements of Brenner tumor. He believed that Brenner tumors arose through a dislocation of similar cells from the primitive wolffian duct. However, although the urinary and the genital anlagen develop in close proximity to each other, direct connection has rarely been proved to exist within the ovary. The third hypothesis, namely, that the teratomatous origin, is based on the fact that about a third of Brenner tumors occur in the walls of mucinous cysts of the ovary. In a few cases there has been uterine bleeding at irregular intervals but the tumor is not known to produce any hormones which could be held accountable for this symptom. In 5 cases reported in the literature, a Brenner tumor complicated pregnancy. Ascites is produced occasionally. In 1 case hydrothorax completed the picture of Meigs' syndrome. One should never forget that certain benign ovarian tumors can imitate malignancy in this way. A surgical diagnosis on macroscopic examination of the specimen is rarely possible, but the general gross characteristics of Brenner tumor are those of a benign neoplasm. Microscopically, the chief danger is in mistaking Brenner tumor for primary or metastatic epithelioma. The predominantly fibrous nature of the growth, the complete absence of mitosis and the peculiar combinations of islands of squamous cells showing central transitions to columnar elements are the salient points of diagnosis.

In discussing the histogenesis of these tumors Danforth[5] believes that most authorities agree that they have as their anlagen the cell rests described by Walthard. In addition, the occasional finding of Brenner tumors in the walls of pseudomucinous cystadenomas of the ovary, and the more frequent finding of pseudomucinous epithelium in Brenner tumors and Walthard rests, have been cited as indications that at least a portion of the pseudomucinous cystadenomas may have their origin in Brenner tumors. If these inferences are true, one might expect to find certain cytologic as well as architectural features common to all 3 structures. The Walthard rest is a small collection of cells which may be found in the cortex or hilus of the ovary, or beneath the serosa or within the mesosalpinx of the fallopian tube. The rests are of 2 types, the solid and the cystic. In the cystic type the central portion of the rest is occupied by a clear space which is said to contain mucin or pseudomucin, colloid, or mixed material. The cystic cavity is ordinarily lined by from 1 to 10 or more layers of cells. The origin of the Walthard rests is obscure. They are stated variously to arise from the celomic epithelium of the developing embryo, from an inflammatory reaction of the peritoneum, from the germinal epithelium and from numerous other structures. The first named is probably most widely accepted. With an oil immersion lens, the most striking feature of the cells is the nucleus, which is not simply round or ovoid, as it has been described, but in addition is seen to be marked or "tagged" in a specific manner. This marking consists of a tiny groove or fold which traverses the long axis of the nucleus in such a manner as to remind one of a coffee bean, or a kernel of puffed wheat. In many of the rests this characteristic marking is present in approximately 9 of 10 nuclei, being evident as a straight, bold line through the long axis, dividing the

nucleus into 2 almost equal halves. As nearly as can be ascertained, this basic pattern is characteristic of one of the flat surfaces of a healthy, non-degenerate nucleus. In these instances the nuclear material is seen to be very finely granular and to contain, generally, 1 or 2 nucleoli. When 2 nucleoli are present 1 usually appears upon either side of the dividing groove. Walthard rests and Brenner tumors bear a strong resemblance to one another, not only in intrinsic architecture, but also, and more especially, in nuclear detail. The basic nuclear type of each is readily identifiable by the presence of a median groove or fold. The deviations from this basic type are described. This nuclear peculiarity is sufficiently constant to be regarded as a fundamental characteristic of both the Walthard rest and the Brenner tumor. Furthermore, its presence in structures appears to strengthen the hypothesis that they may be derived from the same tissue. The presence of the basic nuclear type in many pseudomucinous cystadenomas is of interest in considering the possibility that a small proportion of these tumors may be derived from Brenner cell rests.

Adrenal Rest Tumor. This rare type of tumor is frequently but not always associated with masculinization. Greene and Lapp[9] call attention to the fact that embryologically the ovaries, testes and adrenal cortex have a common origin, being derived from the celomic epithelium of the urogenital fold. This urogenital fold in later embryonic life divides to form the adrenal cortex and the gonads. It is not without possibility, therefore, that misplacement of the cells occasionally occurs in the ovary from the neighboring adrenal anlage. The mere presence of adrenal tissue in an aberrant site does not necessarily mean that the clinical signs of masculinization will always be present. The tendency for aberrant adrenal tissue to become neoplastic cannot be doubted, however. From the recorded cases, no correlation appears to exist between the age of the patient and the occurrence of the tumor. The tumor has been observed at various ages from 3 to 65. The tumor is generally unilateral, varying in size from several millimeters to 3 or 4 cm., occasionally slightly larger. It is most often noted in the hilar region of the ovary, although it may involve the whole ovary by contiguity. It is a solid tumor, often encapsulated, rarely becoming cystic, occasionally showing small areas of hemorrhage and necrosis on cut surface. The external surface is usually smooth. The tumor is generally of soft consistency, and has a characteristic yellow color, resembling closely its analogue, the adrenal. It is probable that most of these tumors are benign, as is true of comparable lesions of the adrenal. Excision of the tumor frequently produces moderate to complete regression of all signs and symptoms. The voice changes, however, usually are permanent. If the hirsutism does not disappear postoperatively, the presence of additional adrenal cortical tissue in other aberrant locations is a possibility. It is interesting to note the sex hormone produced by the adrenal rest cell produces sex characteristics and changes not of the same but of the opposite sex. In the male, the adrenal rest tumor is known to produce a female type of adiposity, breast hypertrophy, at times with lactation, testicular atrophy and loss of libido.

In reviewing 1 case of their own and 13 cases of this type reported in the literature, Kepler, Dockerty and Priestley[16] found that hirsutism was present in all 14 cases and varied in duration from 9 months to 13 years. A masculine pattern of distribution of hair usually was noted. This was emphasized in 4 instances by an observed recession of the hairline along the forehead, with the notation that the patients were partially bald. In 10 of the 14 cases the habitus was described as being of masculine type with pronounced development of the muscles of the shoulder girdle. In 8 of the 14 cases there was a definite and sometimes pronounced gain in body weight. Moreover, in the majority of the observed instances the obesity

was more or less localized to the face, cervical region and pectoral girdle. Blood pressure readings were recorded in 6 of the 12 cases that were reported more recently. In 4 of these cases, hypertension was present with systolic pressures in excess of 140 mm. or diastolic pressures of more than 90 mm. of mercury. In the case they reported, postoperative readings of the arterial blood pressure indicated a moderate drop in both systolic and diastolic pressures from distinctly high preoperative levels. This finding indicates that in some way the ovarian tumor was responsible for the observed arterial hypertension. Diabetes or a diabetic tendency was of relatively frequent occurrence. Hematologic observations suggesting polycythemia vera were unusually common in this group. Size has varied from nodules of microscopic dimensions to masses measuring 16 x 14 x 9 cm. The tumors were for the most part yellowish in color and encapsulation was the rule in practically all recorded instances. Microscopically, the tumors were composed of large, pale, polyhedral, epithelial-like cells disposed in cords and anastomosing strands. Large amounts of intracellular lipoid material were noted in nearly all cases and intercellular glycogen was occasionally found to be present. Like arrhenoblastomas, the adrenal-like ovarian tumors tend to masculinize their hosts but the tendency toward the production of a bizarre type of fat distribution, the occurrence of purplish striæ, arterial hypertension, polycythemia, etc., relate them more closely to adrenal cortical carcinomas from a functioning standpoint. Histologically, the tumors do not appear to arise through luteinization of preëxisting granulosa cell neoplasms and an origin from adrenal cortical rests seems more logical than does a derivation from corpora lutea. An origin by way of teratomatous development likewise remains unproved. Some of the tumors appear to be cytologically malignant and in 1 instance death resulted from metastasis.

Struma Ovarii. The presence of thyroid tissue in an ovarian tumor is not common. Gusberg and Danforth[10] have found only 8 cases over a 20 year period at the Sloane Hospital, representing 2.7% of 297 ovarian teratomata of all types. Of the 8 cases which they report, 7 presented the usual array of clinical symptoms and signs which ordinarily accompany benign ovarian tumors; intermittent abdominal pain, painless pelvic or abdominal masses, and, in 1 instance, acute abdominal pain due to torsion of the pedicle. In these cases, the presence of thyroid tissue is of pathologic interest only. The cystic tumors were generally multilocular, and 3 of the 7 contained epidermoid elements characteristic of the ordinary dermoid cyst. Microscopically, none of these cases showed evidence of hyperplastic changes in the thyroid tissue. The eighth case, however, presented a symptom complex of an unusual nature, the diagnostic and therapeutic implications of which are deemed significant. In this case a huge struma colli, a large struma ovarii and evident thyrotoxicosis were coëxistent. It is unfortunate that the possibility of ovarian struma was not considered and the preliminary work-up carried out with this in mind. That struma ovarii is capable of producing or at least contributing to thyrotoxicosis, is established. It is this ability which distinguished the ovarian struma among all ovarian neoplasms, and removed it from the category of the simple pathologic curiosity. It should be emphasized that cases of functioning ovarian struma may easily escape diagnosis, either through failure to appreciate mild hyperthyroid symptoms, or through chance avoidance of thyroid tissue in the sectioning of large ovarian teratomata. It is of interest that in most of the cases in which such data are available, the ovarian sections have failed to show the presumed microscopic stigmata of hyperthyroidism, despite amelioration of symptoms by removal of the tumor. It would appear reasonable to consider the ovarian struma as a functioning part of the total thyroid tissue of the body, which may react to iodine lack,

to the thyrotropic hormone, or to other stimuli in a manner similar to that of the thyroid gland itself. If this hypothesis is tenable, one might then consider the removal of an ovarian struma as tantamount to subtotal ablation of the thyroid gland.

TERATOMA. In reporting 1 of these interesting tumors, Curtis[4] states that, although encountered in other organs and tissues of the body, teratoma is predominantly an ovarian tumor and it is here that it is found in most developed and characteristic form. It is usually a compact, solid, rapidly growing neoplasm composed of tissues which are frequently wholly undifferentiated, corresponding to various stages of fetal development and revealing only isolated tendency to more completely developed organ-like formation. The material entering into the structure of dermoids and teratoma is the same, all 3 germinal layers represented in both; the differences lie apparently in the tissue of origin and in the fact that dermoids are comprised of mature tissues whereas a teratoma consists of embryonal elements. The great characteristic of teratoma is the loss of proportion in its structure. There is topographic confusion. Opinions differ in judgment of the malignancy of teratoma; it is a growth characterized by capacity for great proliferation, not ascribable to carcinomatous or sarcomatous degeneration but an inherent property of the cells which constitute it. Therefore, it is to be regarded as potentially malignant in all cases, unquestionably malignant in most instances. The tumor is usually nodular or lobulated, often with projecting cysts, of astonishingly large size for so malignant a neoplasm (due to rapid growth?), often the size of a man's head. It may be spherical, ovoid or of ovarian shape, is usually pedunculated, of varied color—gray, yellow, red, blue, brown. The consistency is usually soft, but many are firm. A capsule is usually present but may not be clearly defined. Perforation of the capsule is frequent, but by no means usual. Microscopically, the picture is that of chaos. The tissues are mostly fetal in character, but not entirely and invariably so. It is characteristic for well-differentiated tissues to lie immediately adjacent to lawless and wild areas of potentially or definitely malignant epithelial, endothelial, or sarcomatous pattern. Teratoma is a tumor of childhood and early maturity, mostly before the age of 35. Not more than 5 recorded cases have been found after the menopause. The etiology remains unsolved. The growth must be derived from a cell that can produce all 3 embryonic layers. Only 2 theories of origin are prevalent: that isolated blastomeres are the source of these trigerminal growths or that they arise from primitive unfertilized ova.

In presenting 32 collected cases, in which the outcome is known, including 2 cases of his own, Smeltzer[25] found that 21 (65%) are dead while the other 35% have survived from 1 to 10 years. It was noted that the tumors were practically always pedunculated and the surgical treatment carried out was simple excision of the pedunculated tumor or adnexa on that side. The high rate of recurrence of tumor and death indicates that a more extensive surgical procedure is indicated. These tumors are usually well encapsulated. There is ordinarily a well-formed pedicle; seldom is there any more than very fine adhesions to the surrounding organs. The findings of extension or gross metastasis is rare at the time of the first operation. To all appearances when the abdomen is first opened the operator is dealing with a benign tumor, or at least one of very low malignancy. These observations, added to the fact that the patient is young, make it very difficult to proceed with radical surgery. The pedunculated tumor recurs at the site of the original lesion. Later it spreads from this area by extension as well as metastasis. However, metastasis seems to be a late manifestation. This observation further emphasizes the need for wider excision at the time of removal of the primary growth. The effect of Roentgen ray therapy upon this type of tumor is debatable. These

cases should be given Roentgen ray in therapeutic amounts immediately after the primary operation. How effective Roentgen ray will be in preventing a recurrence he does not know but he does not believe it is beneficial after recurrences are present. He believes that more emphasis should be placed upon a wider excision of the original growth. This means removal of all the pelvic viscera as widely as the operator's experience allows him to dissect. The operation should then be followed by Roentgen ray in the amount compatible with the patient's age and size. Girls with teratoma should be treated in a manner similar to adult women with carcinoma of the ovary.

CARCINOMA. All are agreed that one of the most effective weapons we have against any cancer is prevention or at least early detection and removal. Ovarian cancer is notoriously "silent" in its early stages and we all have had the experience of Crossen[3] who states that patient after patient is seen with an extensive growth of long duration but with only a short period of local symptoms. The first visit to the physician shows a large advancing carcinoma causing only such minor disturbances that the patient hardly notices them. Thinking back, when questioned, she recalls that the abdomen has been a little larger for a year or so or that there was bloating or some frequency of urination, but only in the last few weeks was there enough disturbance to make her feel that perhaps an examination was advisable. He believes the greatest contribution the physician can make toward the lessening of these fatalities is the practical application in his daily work of 2 rules: (1) removal of the involuting ovaries whenever the abdomen is opened at any age and under circumstances which permit such removal; (2) insistence on regular periodic pelvic examination of patients who ask us to assume responsibility in regard to their health. The menopause (complete cessation of menstruation) occurs usually between the ages of 44 and 47, with exceptions somewhat below and above these limits. The climacteric (gradual involution of the ovaries) begins 2 or 3 years before the menopause and extends some years after it. Though there is considerable individual variation as to age of onset of ovarian involution, a reasonable rule would be to apply this safety measure in all abdominal operations when the patient has reached the neighborhood of the age of 42. The involuting ovaries have fulfilled their reproductive and endocrine functions. They are no longer an important part of the economy but vestigial structures which carry a special tendency toward cancer—and toward a particularly dangerous form of cancer, in that it develops to an incurable stage without warning symptoms. The realization of the necessity of adopting this safety measure has been obscured and delayed by the various arguments for retention of an ovary. In the first place, there is the excellent surgical rule to do no more operating than necessary—to remove no structure without a definite reason of sufficient importance to justify the additional operative risk and any probable upset in physiology. Again, the great importance of the ovaries during the span of their physiologic activity projects about them a halo which tends to obscure the fact that they are only temporary organs that cease to function after a certain period. Again, there is the desire to lessen the hot flushes and other disturbances of ovarian cessation by preserving ovarian tissue even though it is functioning only partially. Still again there is the natural desire of the patient that an ovary be saved if practicable. These are all valid arguments and have long influenced decisions, but through careful observation and bitter experiences he has come to realize that the danger of cancer development in the involuting ovary outweighs all these arguments for leaving an ovary in an abdominal operation in the age of involution. In the period from 40 to 60 years of age pelvic examination is advisable every 6 months instead of once yearly, as may suffice before and after that period.

Symptomless onset and symptomless progress to incurability constitute the natural history of ovarian carcinoma. Earlier discovery is due to some incidental associated condition or to a pelvic check-up examination. The aggregate of deaths from this cause is large, much larger than is generally appreciated. To the known cases must be added the unrecognized ones with death certificate designations of "ascites" and "abdominal cancer." A large proportion of the cases of general abdominal carcinosis originate in an ovary. The silent character of the onset and progress of ovarian cancer seals the doom of patients with this condition unless measures that are really effective against the serious difficulties of the situation are put into practice.

In reviewing the end-results in a series of 138 patients with ovarian carcinoma operated upon at Roosevelt Hospital in New York, Taylor and Greeley[26] found an "absolute" 5 year cure rate of 15.2%, when all cases are considered and the lost cases are counted as dead. It is well recognized that the gross extent of the ovarian carcinoma at the time the operation is undertaken is the most important single consideration in prognosis. If one defines an operable case as one in which all cancer was apparently removed, the operability of this series was 31%. The known cures in this operable group were 45.5%, while if the many cases untraced for the necessary 5 years, but free of disease when last seen, be excluded, the 5 year cure rate in the operable group becomes 58.8%. The other side of the picture is as gloomy as this is encouraging, for of the 94 cases in which malignant tissue was left behind at the conclusion of the operation or which was recurrent, only 2 have survived the 5 year period. The cancers of the ovary are distinguished by the diversity of their cells of origin, and evidence has been presented in the literature to show that certain of the special types, such as the granulosa cell tumors and dysgerminomas, have a relatively favorable prognosis. The grade of malignancy in ovarian cancer is of enormous prognostic significance. The classification of 88 cases of ovarian adenocarcinoma indicates only 2 cures among 52 undifferentiated types, whereas among 36 so-called Grade 1 cases there were 12 cures. In a series of cystadenomas and adenocarcinomas of the ovary, the morphologic transition from the benign to the malignant takes place almost imperceptibly. No pathologist has had the experience to place the line of division exactly. Difference of opinion as to what histologic features justify the classification of some of these borderline tumors as benign or malignant is probably the most important variable governing the reported figures on cures of ovarian cancer. A slight change in conception of the morphologic criteria of malignancy in the cystic tumors of the ovary appears to them largely to explain the change in their own figures from the 8.3 cure rate of their 1934 report to the 15.2% noted in the present article. It does not appear that radiation, as given at the Roosevelt Hospital, has materially affected the average duration of life in cases of ovarian cancer.

The seriousness of ovarian malignancy has been given considerable thought by Goodall[8] who feels that there is no clinical criterion by which one can distinguish a non-malignant from a malignant ovarian growth. Especially is this true while the malignant growth is still limited to the ovary and encapsulated. Yet this is the only period in which malignancy can be dealt with satisfactorily. Ovarian new-growths are unfortunately singularly free from symptoms. Even the menstrual cycles and characters are seldom disturbed. The advent of pain, or of free fluid in the abdomen are too often the heralds of ineradicable extensions. When upon opening the abdomen, the case presents a definite peritoneal involvement, he knows of no rule which can be laid down to guide the surgeon. Only experience can be a safe judge. In these circumstances both ovaries are generally involved, one higher up, and the other bound down by

peritoneal extensions in the pouch of Douglas. When, however, the ovarian growths can be removed without too much risk, even at the expense of considerable difficulty, it is thought that the period of life is lengthened. This is a debatable point, for no one can state what the tempo of that tumor was before operation, and what will be its rate of growth afterward. When the case is operable it is his policy to remove both ovaries whenever there is undoubted malignancy of one of them. This is not so radical a procedure as one might suspect. Most of these patients are in their late thirties or older, and spaying, as a rule, does not involve any grave consequences. It would seem that deep Roentgen ray application should find in malignant ovarian disease a field of great usefulness, but he has found deep Roentgen ray therapy singularly inefficient in the cure or alleviation of cases of peritoneal involvement. It is his conviction that Roentgen rays not only do not improve, but have almost invariably broken down the patient's health and hastened death. He concludes that the only hope for a patient suffering from incipient malignancy of the ovaries lies in early extirpation, before the disease has spread beyond the confines of the ovary. This will necessitate exploratory operation upon any suspicious tumor of the ovaries. Our attitude toward ovarian newgrowths must be somewhat akin to the position we adopt toward tumors of the breast.

A somewhat more optimistic note as to the value of Roentgen therapy is expressed by Walter, Bachman and Harris[27] who have reviewed the literature on postoperative radiation therapy of ovarian carcinoma and present 124 additional cases treated by surgery alone or by surgery and postoperative radiation. They believe that failure to classify the cases according to stage of progression has made evaluation of the early results of therapy difficult. The classification they employ groups the cases into 4 stages: (1) a primary unilateral and completely removable tumor with no visible metastases, (2) the presence of local metastases which are completely removable with the primary tumor, (3) the presence of local metastases which are only partially removable with the primary tumor, and (4) cases with advanced carcinomatosis peritonei for which exploratory celiotomy or removal of large tumor masses are diagnostic and palliative measures. In Stage 1 and 2 cases reported in the literature the supplementary use of radiation therapy did not significantly alter the five year survival rate, but the increased number of five year survivals of Stage 3 cases in the irradiated group appears to be of statistical significance. The prognosis in Stage 4 is extremely grave.

Further value of Roentgen therapy is suggested by Parks[24] who reports 3 cases of papillary cystadenocarcinoma of the ovary, inoperable because of massive infiltration into the surrounding structures, which were apparently made operable by deep Roentgen ray therapy. In all 3 cases the neoplasm was limited to the abdominal cavity. The Roentgen ray profoundly affected the gross appearance of the tumors, but caused very little change in the microscopic picture. Two of the patients are alive after 8 and 12 years, respectively; the third succumbed after 5 years of an apparently unrelated carcinoma. Deep Roentgen ray therapy in the 3 cases reported caused the papillary excrescences and transplants to shrink and the entire mass to diminish in size, thus making operation easier. This study indicates that it is unwise to persist in doing a difficult primary operation. In some cases of massive infiltration, it may be safer to take a biopsy, close the abdomen, give deep Roentgen ray and perform a second operation at a later time.

ADENOACANTHOMA. A rare type of cancer, composed of both glandular and squamous elements is termed adenoacanthoma. In reporting 2 such lesions in the ovary, Melody, Faulkner and Stone[23] were unable to find another instance of primary adenoacanthoma of the ovary in the literature. They state that the histo-

genesis of this type of lesion is much disputed. Some believe that the "epidermization" seen in fundal adenoacanthoma is the result of metaplasia of the cylindrical to the squamous type of epithelium. A study of cervical biopsy material reveals the very great frequency of metaplasia of the normal columnar to the squamous type of epithelium, in inflammatory lesions of the cervix uteri. Moreover, it is recognized that the germinal epithelium covering ovaries which are involved in chronic perioöphoritis occasionally does undergo squamous metaplasia. Then, there is the condition known as cystic fibrosis of the pancreas in which, due to the impaired absorption of fat-soluble vitamin A, there is a pronounced squamous metaplasia of the bronchial mucosa. It would appear, therefore, that squamous metaplasia is really of rather frequent occurrence in a wide variety of pathologic processes, running the gamut from chronic inflammatory lesions, and a vitamin deficiency state, to frank neoplasms. It seems entirely tenable, therefore, to assume that the squamous elements in the ovarian adenoacanthomas are the result of the ubiquitous process of metaplasia. Another plausible hypothesis for the presence of squamous epithelium in ovarian carcinoma is the supposition that such may result from Walthard's islands which are thought to result from the "invaginations of celomic epithelium." The manifold possibilities of celomic epithelium on differentiation are well known. It well may be that the origin of the squamous elements in ovarian acanthoma is identical with the generally accepted theory of histogenesis of Brenner tumor, *viz.*, Walthard's cell rests. The authors, however, incline to the view that the squamatization seen in the tumors described is the result of metaplasia.

KRUKENBERG TUMOR. In presenting a study of 44 cases of Krukenberg tumors from the Mayo Clinic, Leffel, Masson and Dockerty[18] state that most workers agree on the fact that this is usually a secondary tumor and no description of it has surpassed that originally given by Krukenberg. He stated that the tumor was of moderate size; it was nodular yet it possessed a smooth surface. Adhesions were usually absent in such cases but ascites was often found. The tumor was usually bilateral, usually solid, occasionally cystic and the general form of the normal ovary was usually maintained. The cut surface had a myxomatous appearance. Microscopically, Krukenberg described "signet-ring" cells surrounded by a fibrous stroma. He recognized the picture as one of undoubted malignancy and considered the lesion as primary in the ovaries. However, there is as yet no general agreement as to what constitutes a Krukenberg tumor; as to how metastasis occurs; as to whether a primary ovarian carcinoma may be impossible to distinguish from a Krukenberg tumor; as to whether the metastasis is in any way selective; or on how the lesion should be treated. They feel that these tumors should be described, like other metastatic tumors, merely as metastatic carcinoma of the ovary. Realizing, however, that the term "Krukenberg's tumor" will continue to flourish in medical literature, they contend that it should include all metastatic adenocarcinomata of the ovary. There is no real difference between metastatic adenocarcinoma of the ovary and metastatic adeno-"colloid" carcinoma of the ovary, save for the presence of mucus in the latter. However, if this difference were overlooked, not even the remotest reason would ever exist to use the term "Krukenberg's tumor." Metastasis may occur in 4 ways: (1) spread by peritoneal sedimentation, (2) spread by lymphatic channels which must include retrograde spread, (3) extension by continuity, and (4) spread by way of the blood stream. The treatment of this tumor depends on many factors, chief of which are the patient's general condition and the extent of the growth. Given a patient who is a poor surgical risk or one showing evidence of extensive metastasis, surgical treatment is contraindicated, save for the relief of an obstruction of the gastro-intestinal tract. Given a patient

who is a good surgical risk without extensive carcinomatosis, the uterus, tubes and ovaries should be removed. This procedure is justified for 3 reasons: (1) the pathologist's diagnosis may be wrong, (2) the remaining days or months which the patient has to live will be more comfortable without the presence of a huge pelvic mass and abundant ascites, (3) the increased mortality and morbidity associated with this procedure are not great enough to warrant not attempting to give the patient the comfort that would result from such a procedure. Circumstances may justify leaving the uterus intact but an apparently atrophic ovary should never be left intact. Every surgeon cannot have a pathologist at his side, particularly one who is experienced with the diagnosis of fresh tissue. A good general rule, in this case, is to remove both ovaries when a solid tumor is found involving either one, particularly if the patient is past or near the menopause. The treatment of the primary lesion usually depends upon the site. All things being equal, the surgeon is justified in being more radical when the primary lesion is in the colon than when it is elsewhere, because of the frequent relatively low grade of these lesions.

Fibroma. Although ovarian fibroma is a benign lesion, it is the second most common solid tumor of the ovary. In a study of 283 cases from the records of the Mayo Clinic, Dockerty and Masson[7] never found a fibroma before puberty, which they believe indicates an origin possibly based on a desmoplastic reaction to the hemorrhage of ovulation or ovarian endometriosis. Fibroma did not produce any specific diagnostic symptoms and rarely was it possible for the clinician to go further than to diagnose an ovarian tumor. Abdominal ascites (51 cases) and hydrothorax (2 cases—syndrome of Meigs) suggested the existence of a malignant process but the patients never presented the picture of cachexia. The complications of these tumors were chiefly those associated with twisting of the pedicle of the tumor—a phenomenon which rarely occurred until the tumor outgrew the confines of the true pelvis. Pathologically, most of the tumors were solid throughout, white and usually invested by a smooth capsule free from adhesions. Many of the tumors were edematous and a number of these had undergone degenerative changes with central cysts or "geodes." The common denominator relating to both ascites and formation of cysts was a weeping edema effected through partial obstruction of the venous return. In 90% of cases the tumor was unilateral. Bilateral fibroma-like tumors sometimes proved to be metastatic tumors of the Krukenberg type with the primary neoplasm most frequently in the stomach. A yellowish color suggested theca cell tumor, especially in cases in which the uterus was large and postmenopausal bleeding was noted clinically. In others the yellow color resulted from fatty metamorphosis. A grayish brown color and firm consistency were noted in several tumors that later proved to be of the Brenner type. A brownish color and soft consistency indicated malignant change, which occurred in 1% of the tumors studied. Degenerative changes, such as fatty, fibrous hyaline and calcareous, took positions of importance secondary to the phenomenon of intercellular edema, which correlated more universally than did gross edema and formation of cysts with the clinical production of ascites.

In an effort to explain how fluid gets into the pleural cavity in some cases of ovarian fibroma (Meigs' syndrome), some interesting studies were made by Meigs, Armstrong and Hamilton.[22] In 2 patients 2 cc. of sterile India ink was injected in the abdomen, and chest taps performed later. In each instance the fluid in the chest showed the same concentration of India ink as in the abdomen. That the India ink did not arrive in the pleural fluid by way of the blood stream was considered established by study of the blood shortly after injection of the abdomen with India ink. In the 2 patients the blood showed no evidence of India ink in the

leukocytes on microscopic examination. This experiment is suggestive evidence that the abdominal fluid in these patients arrives in the chest by the same pathway as the India ink, or *vice versa*. The probability is that the pathways are lymphatics, first through the interstices of the cells under the diaphragm, thence to the supradiaphragmatic lymphatics and thence into the chest. The passage of particulate carbon is of considerable interest when considered with relevance to the mechanism of hydrothorax in conjunction with ascites in certain conditions other than Meigs' syndrome. Statistical considerations enhance this interest for Meigs' syndrome is rare in comparison with ovarian fibromas with ascites alone. So, likewise is hydrothorax and ascites rare in comparison with Laennec's cirrhosis with ascites alone. It may be that hydrothorax is found in conjunction with ovarian fibroma or portal hypertension, in those few patients who also have sufficient congenital mechanical communication between peritoneum and pleura. Extension of this hypothesis leads to investigation of the possibility of such communication in conditions where the basis of fluid in both cavities is more readily explicable, *e. g.*, cardiac decompensation and metastatic carcinoma. Initial experiments in this investigation have been completed. In 2 patients, 1 with carcinomatosis, the other with Laennec's cirrhosis, particulate carbon injected into the pleural fluid failed to attain the peritoneal fluid within 24 hours. At first glance, this result might be taken to indicate that no communication exists in these instances. However, it should be noted that in 2 cases of Meigs' syndrome, only communication from abdomen to chest, not from chest to abdomen, has been demonstrated. It remains for joint investigation by thoracic surgeons and others to demonstrate the presence of diaphragmatic perforations of small or large size, the presence of the rarely reported pleuroperitoneal tubes, and to determine the direction and degree of penetrability of diaphragmatic lymphatics.

REFERENCES

(1.) **Banner, E. A.**, and **Dockerty, M. B.**: Surg., Gynec. and Obst., **81**, 234, 1945. (2.) **Brentnall, C. P.**: J. Obst. and Gynec. Brit. Emp., **52**, 235, 1945.

(3.) **Crossen, H. S.**: J. Am. Med. Assn., **119**, 1485, 1942. (4.) **Curtis, A. H.**: Surg., Gynec. and Obst., **81**, 504, 1945.

(5.) **Danforth, D. N.**: Am. J. Obst. and Gynec., **43**, 984, 1942. (6.) **Dockerty, M. B.**: Internat. Abstr. Surg., **81**, 179, 1945. (7.) **Dockerty, M. B.**, and **Masson, J. C.**: Am. J. Obst. and Gynec., **47**, 741, 1944. (8.) **Goodall, J. R.**: Am. J. Obst. and Gynec., **43**, 210, 1942. (9.) **Greene, H. J.**, and **Lapp, W. A.**: Am. J. Obst. and Gynec., **47**, 63, 1944. (10.) **Gusberg, S. B.**, and **Danforth, D. N.**: Am. J. Obst. and Gynec., **48**, 537, 1944.

(11.) **Henderson, D. N.**: Am. J. Obst. and Gynec., **43**, 194, 1942. (12.) **Hodgson, J. E.**, **Dockerty, M. B.**, and **Mussey, R. D.**: Surg., Gynec. and Obst., **81**, 631, 1945.

(13.) **Johnson, J. R.**, and **Dockerty, M. B.**: Proc. Staff Meet. Mayo Clin., **20**, 120, 1945. (14.) **Jones, G. E. S.**, and **TeLinde, R. W.**: Am. J. Obst. and Gynec., **50**, 691, 1945.

(15.) **Kanter, A. E.**, and **Klawans, A. H.**: Am. J. Cancer, **40**, 474, 1940. (16.) **Kepler, E. J.**, **Dockerty, M. B.**, and **Priestley, J. T.**: Am. J. Obst. and Gynec., **47**, 43, 1944. (17.) **Krock, F.**, and **Wolferman, S. J.**: Ann. Surg., **114**, 78, 1941.

(18.) **Leffel, J. M., Jr.**, **Masson, J. C.**, and **Dockerty, M. B.**: Ann. Surg., **115**, 102, 1942. (19.) **Long, C. H.**, **Ziskind, J.**, and **Storck, A. H.**: Surg., Gynec. and Obst., **73**, 811, 1941.

(20.) **McGoldrick, J. L.**, and **Lapp, W. A.**: Am. J. Obst. and Gynec., **48**, 409, 1944. (21.) **Mechler, E. A.**, and **Black, W. C.**: Am. J. Pathol., **19**, 633, 1943. (22.) **Meigs, J. V.**, **Armstrong, S. H.**, and **Hamilton, H. H.**: Am. J. Obst. and Gynec., **46**, 19, 1943. (23.) **Melody, G. F.**, **Faulkner, R. L.**, and **Stone, S. J.**: Am. J. Obst. and Gynec., **49**, 691, 1945.

(24.) **Parks, T. J.**: Am. J. Obst. and Gynec., **49**, 676, 1945.

(25.) **Smeltzer, M.**: Am. J. Obst. and Gynec., **41**, 616, 1941.

(26.) **Taylor, H. C., Jr.**, and **Greeley, A. V.**: Surg., Gynec. and Obst., **74**, 928, 1942.

(27.) **Walter, R. I.**, **Bachman, A. L.**, and **Harris, W.**: Am. J. Roentgenol., **45**, 403, 1941.

PHYSIOLOGY

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Postburn Azotemia, Its Significance as Criterion of the Severity of Thermal Injury and of the Efficacy of Fluid Therapy. OTTO ROSENTHAL, M.D., and MILES D. MCCARTHY, PH.D. (Harrison Dept. of Surg. Res., Univ. of Penna.). Non-protein nitrogen, urea nitrogen and amino nitrogen were determined in the plasma of rats subjected to standard burns of known lethality (M. D. McCarthy, *J. Lab. and Clin. Med.*, **30**, 1027, 1945). The difference between non-protein nitrogen and the sum of urea and amino nitrogen was designated as undetermined nitrogen.

Following the scalding, 1 group of rats received no treatment while others were transfused with physiological saline solution, normal rat plasma, human albumin or gelatin.

The increases in the undetermined nitrogen and amino nitrogen of plasma reflected the severity of burn whereas the urea levels did not. The proportionally largest increase occurred in the undetermined nitrogen fraction, the levels of which furnished a sensitive criterion of the severity of burn. This finding is in accord with the experience in man (J. Walker, Jr., AM. J. MED. SCI., **209**, 413, 1945).

The degree of permanent reduction of the increased amino nitrogen and especially of the undetermined nitrogen levels of plasma provided an index of the efficacy of fluid replacement therapy, whereas the response of the urea nitrogen levels was too slow and too irregular to be of use for this purpose.

The effectiveness of fluid replacement therapy in permanently reducing the elevated undetermined nitrogen levels was not clearly related to the relief of hemoconcentration. It is suggested that a renewed rise of the undetermined plasma nitrogen levels in spite of nearly normal hematocrit values is an indication of a returning tissue anoxia due to a diminution of the actively circulating rather than of the total blood volume.

Cerebral Blood Flow and Metabolism in Patients With Increased Intracranial Pressure. HENRY A. SHENKIN, M.D., SEYMOUR S. KETY, M.D., FRANCIS C. GRANT, M.D., and CARL F. SCHMIDT, M.D. (Depts. of Pharmacol. and Neurosurg., Univ. of Penna.). Observations on the cerebral blood flow utilizing the nitrous oxide method of Kety and Schmidt, cerebral metabolism, cerebrospinal fluid pressure and blood gas concentrations were made on 12 patients, 9 of whom had increased intracranial pressure.

A reduction in cerebral blood flow is well correlated with increased intracranial pressure due to brain tumor. The average cerebral blood flow in the 9 patients with increased intracranial pressure was 52.7 cc. per 100 gm. of brain per minute. The normal cerebral blood flow has been found to be an average of 70 cc./100 gm./min. determined by the same technique.

Cerebral oxygen consumption was decreased by increased intracranial pressure but was not correlated to the degree of increased pressure. The average oxygen consumption of patients with increased intracranial pressure was 3.7 cc./100 gm./min., as compared with an average normal of 4.3 cc./100 gm./min. Alteration in the states of consciousness of the patients seemed better related to the decrease in cerebral metabolic activity than to the decrease in cerebral blood flow.

The mean arterial blood pressure (aver. 115 mm. of mercury) was unequivocally increased in all patients in this series with increased intracranial pressure and cor-

related well with the decrease in cerebral blood flow.

In those patients with high increased intracranial pressure and markedly reduced cerebral blood flow, rapid reduction of the increased intracranial pressure by ventricular drainage or 50% glucose solution given intravenously did not improve the cerebral blood flow. In patients with moderately increased intracranial pressure and moderately decreased cerebral blood flow, 150 cc. of 50% glucose solution given intravenously markedly increased cerebral blood flow. Ventricular drainage has not been applied, as yet, to patients in the latter situation.

Biological Precursors of Uric Acid Carbon. JOHN C. SONNE and JOHN M. BUCHANAN, PH.D. (Dept. of Physiol. Chem., Univ. of Penna.). A study of the biological precursors of uric acid carbon has been made by administering to pigeons compounds labeled with C^{13} (*i. e.*, isotopic $NaHCO_3$, carboxyl-labeled acetate, lactate and glycine and lactate labeled in the α or β positions). Uric acid was isolated from the excreta, purified and degraded by chemical methods in such a manner that each of its 5 carbon atoms could be obtained separately. It was found that CO_2 is the precursor of carbon 6 of uric acid; the carboxyl carbon of acetate is the precursor of carbons 2 and 8; and the carboxyl carbon of glycine is the precursor of carbon 4. The carbon atoms of lactate were also incorporated into uric acid but in a smaller order of magnitude than the carbons of CO_2, acetate and glycine. Carbons 4 and 5 of uric acid were derived from the carboxyl and α (or β) carbons of lactate respectively. It is thought that glycine may be formed from lactate by reactions similar to the conversion of serine to glycine (D. Shemin, *J. Biol. Chem.*, **162**, 297, 1946).

In a supplementary experiment it was shown that the carboxyl carbon of acetate is not a direct precursor of urea carbon in the rat.

From the data presented, the conclusions were drawn that glycine and acetate are not interconvertible in the metabolism of the pigeon and that the precursors of urea carbon in the rat and of ureide carbon in the pigeon are different.

Permeability Methods for the Recognition of Abnormal Erythrocytes. M. H. JACOBS, PH.D., W. J. BROWN, M.D., DOROTHY R. STEWART, PH.D., and L. J. KIMMELMAN (Dept. of Physiol., Univ. of Penna.). In the usual clinical fragility test with hypotonic salt solutions conditions of osmotic equilibrium are observed. These are strongly influenced by pH, temperature and other factors, and require an inconveniently long time for their attainment. In the present method, which utilizes the characteristic permeability of erythrocytes to solutes such as glycerol and thiourea, osmotic hemolysis also occurs, but the attainment of an equilibrium condition is unnecessary, and a time of 3 minutes usually suffices for a test. The results are also more reproducible and they demonstrate abnormalities more clearly than do those obtained by the older method.

The blood is collected without an anticoagulant in 0.9% NaCl buffered with phosphate at pH 7.4. After suitable adjustment of the opacity of the resulting suspension of erythrocytes, it is mixed with the hemolytic solution in such proportions that hemolysis takes place in one or the other of the following solutions: (1) 0.3 M glycerol, 3 parts; 0.9% NaCl, 2 parts; or (2) 0.3 M thiourea, 4 parts; 0.9% NaCl, 1 part. The solution containing glycerol must be free from copper. The course of hemolysis is preferably followed by a photoelectric method which yields a permanent photographic record for analysis. In an alternative method hemolysis is stopped by osmotic means at selected points, and the hemoglobin previously liberated by the cells is then

measured. In a much simplified method the time required to reach a chosen degree of hemolysis is determined.

When studied by any of these methods, normal blood shows certain relatively constant properties, and departures from the latter are easily recognized. Characteristic retardations of hemolysis have been found in primary pernicious anemia, sickle-cell anemia, obstructive jaundice, and advanced carcinoma; equally characteristic accelerations have been obtained in hemolytic anemia and during the aging of bank blood.

BOOK REVIEWS AND NOTICES

SHOCK TREATMENTS AND OTHER SOMATIC PROCEDURES IN PSYCHIATRY. By LOTHAR B. KALINOWSKY, M.D., Research Associate in Psychiatry, College of Physicians and Surgeons, Columbia University, and New York State Psychiatric Institute and Hospital; Assistant Neurologist, Neurological Institute of New York; and PAUL H. HOCH, M.D., Assistant Clinical Psychiatrist, New York State Psychiatric Institute and Hospital; Instructor in Psychiatry, College of Physicians and Surgeons, Columbia University. Foreword by NOLAN D. C. LEWIS, M.D. Pp. 320. New York: Grune & Stratton, 1946. Price, $4.50.

SHOCK treatments have been employed for more than 10 years. The chapters are: Historical Developments; Insulin Shock Therapy; The Convulsive Therapies; Combined Insulin-Convulsive Treatment; Other Somatic Neurological Treatments and Their Relation to Shock Treatments; Prefrontal Lobotomy and Its Relationship to Shock Therapy; Theoretical Considerations.

Insulin shock therapy has not fulfilled early expectations; small doses stimulate the appetite and it is a useful sedative. Metrazol as a convulsive was extensively used for a time, but intravenous administration is difficult and frequent fractures a disadvantage. With electro-shock, the current is under full control and the effect is immediate. Sodium amytal affords sedation and removes inhibitions. Continuous sleep may be produced by the barbiturates with best results obtained in mild excitements. Induction of malaria in paretics has long been in use; such residual symptoms as sometimes persist, may be cleared through shock therapy; possibly penicillin may prove the best agent with which to attack paresis. Refrigeration therapy is dangerous and has been abandoned. When shock treatments fail, beneficial effects may be obtained through lobotomy in some schizophrenics, the psychoneuroses and less frequently in involutional depressions; this does not effect a cure, but symptoms may be relieved through removal of the emotional impact.

N. Y.

ESSENTIALS OF NEURO-PSYCHIATRY. By DAVID OLKON. Pp. 310. Phila., Lea & Febiger, 1945. Price, $4.50.

THE author has attempted, in a small volume, to cover the many clinical conditions which constitute the field of Psychiatry. He gives brief descriptions of the ordinarily accepted groups of mental and emotional disorders. He has devoted a full chapter to his own personal observations of the capillary bed and brings together his concepts of this experience in the mentally diseased.

The book is well-written and interestingly illustrated. However, it seems to the Reviewer that there is a marked disproportion in the material presented. The earlier chapters on genetics and other factors which the author feels are related to development of the personality would seem to be unnecessary. Emphasis is often misplaced. For instance, the author dismisses the immense problem of homosexuality in 1 paragraph; yet, there are 6 pages on "Transvestitism." His remarks on onanism would not be acceptable to most schools of Psychiatry today. Similar misconceptions and disproportions occur throughout the book.

Also, it seems to the Reviewer that the whole pattern of the book leads to confusion because of no definite integration of parts; its value to the medical student and to the men active in the field of Psychiatry would

seem to be slight and I doubt if it would add very much to the general medical man's concepts of Neuropsychiatry. G. S.

MOTOR DISORDERS IN NERVOUS DISEASES. By E. HERZ and T. J. PUTNAM. Pp. 184. New York: King's Crown Press, 1946. Price, $3.00.

THE methods of visual teaching used by the Services during this War will have inevitable extension into civilian medical pedagogy. This little book is one illustration of this trend, as it was prepared as a descriptive syllabus for "study, before and after viewing a projection of films" on the various disorders of the motor system. It is a description of disorders of gait, coördination, reflexes and of the mechanisms concerned with eye movements and other disorders of function of the nervous system.

It is illustrated from the films, in part. Needless to say, these are much less effectual than seeing them projected. A number of other diagrams of anatomic nature are included from various sources. The combination of the book and films will undoubtedly provide an interesting introduction to motor disorders. G. G.

AMBULATORY PROCTOLOGY. By ALFRED J. CANTOR, M.D., Associate Proctologist, Kew Gardens General Hospital, Long Island, N. Y. With a Foreword by BEAUMONT S. CORNELL, M.D., Editor, *American Journal of Digestive Diseases*. Pp. 524; 347 special drawings on 275 figures. New York: Hoeber, 1946. Price, $8.00.

THE wide scope of this book stems from the author's belief that proctology should include all colonic pathology and not simply anorectal lesions. The introductory chapters on clinical anatomy, diagnostic methods, anesthesia and preoperative and postoperative management deal entirely with anorectal disease. Subsequent sections, devoted to specific lesions of the anus and rectum, contain good discussions of etiology and pathology and practical and detailed descriptions of therapeutic operative procedure. The chapter on pruritus is particularly complete and features a favorable description of the author's special therapeutic procedure, tattooneurotomy. The remainder of the volume deals in detail with lesions invading the entire colon (colitis, venereal diseases, diverticulitis, benign and malignant tumors). Here again etiology and pathology are fully discussed and both medical and surgical therapy is presented.

Numerous good illustrations are valuable adjuncts to the descriptions of the pathologic conditions and the operative techniques.

This is a comprehensive and useful text for anyone interested in the diagnosis and treatment of diseases of the colon, rectum and anus. W. F.

PHYSICAL CHEMISTRY FOR PREMEDICAL STUDENTS. By JOHN PAGE AMSDEN, Professor of Chemistry, Dartmouth College. Pp. 298; 53 ills. New York and London: McGraw-Hill (International Chemical Series), 1946. Price, $3.50.

THE author has written a short, well-organized and readable elementary text on physical chemistry. As the title suggests, the exposition of the subject is with a view towards the requirements of premedical students. There has been a need for properly oriented courses for premedical students, not only in physical chemistry but in elementary organic chemistry as well.

From the present Reviewer's standpoint the volume is marred only by the continued use of time-worn "problems." The solution of problems is essential in the understanding of applied physical chemistry; but the Reviewer has failed to find cogent problems with a definite biologic bias. For example, the question is asked "At what temperature will benzene boil on top of this mountain" (at reduced atmospheric pressure)? How much more interesting and pertinent it would be not only for premedical students, but for all interested in aviation at high altitudes, etc., if this problem were redressed in a form to apply to the gas exchange of man. It is hoped that in a second edition of this little book, the text may be more obviously directed towards the needs of premedical students by the choice of apt applications. D. D.

ADVANCING FRONTS IN CHEMISTRY. Vol. I. High Polymers. Edited by SUMNER B. TWISS, Department of Chemistry, Wayne University. Pp. 196; liberally illustrated. New York: Reinhold, 1945. Price, $4.00.

THIS short monograph, with papers by 10 individual contributors, is the first of a

series of lectures sponsored by Wayne University under the direction of N. E. Gordon.

The "high polymers" to which the book is largely devoted are rubbers, plastics and fibers. These substances have very large molecular weights and possess high degrees of polymerization (*i. e.*, are composed of some 150 to 10,000 units). Their growing importance in industry is generally recognized. However, it may be well to point out (as one of the contributors has done) that beyond the realm of commerce lie the tissues of plants and animals, and their component structures—proteins, nucleic acids, glycogen, starch and cellulose—are all polymeric. Thus, it is probable that the chemistry of high polymers will develop implications for the biologist and physician; one need merely cite the recent development of fibrin film.

Among the problems dealt with is the phenomenon of aggregation. This is recognized to occur in proteins and glycogen. While biologic applications are only incidental and but lightly touched in the presentation, the monograph will make interesting reading to those concerned with the "advancing fronts in chemistry." D. D.

Rehabilitation. Its Principles and Practice. By John Eisele Davis, M.A., Sc.D., Veterans Administration Facility, Perry Point, Md. Pp. 264; 9 charts and 6 tables. New York: Barnes, 1946. Price, $3.00.

Through the ravages of modern warfare, women and children of all ages as well as men now become its victims, with most of the neuroses continuing to develop for many years after hostilities have ceased. The rehabilitation of those thus handicapped is admirably discussed in the following chapters: Effect of War and Depression; The Psychiatric Approach; Types and Disease Entities; The Psychological Approach; Interest and Effort Theories; Elemental Principles of Mental, Nervous and Physical Reconstruction; Modern Methods; Therapeutic Objectives and Results; Handicraft, Education and Art.

If the psychotic patient is not really dangerous, all possible freedom should be allowed as he engages in work and play activities suited to his physical, intellectual and emotional state. In psychoanalysis the basic thought is that the unconscious mind exerts a profound influence upon our behavior. In the psychologic approach, the worker deals "not with problem cases, but with persons with problems." Psychologic tests are mostly objective and mostly standardized observation of the subject's behavior. Occupational therapy includes handicraft, creative arts, recreation and education. Psychodramatics are important and interesting; among other advantages are the dressing up which causes the patient to feel important, emotional outlet is provided, identification and re-identification of the individual with other personages, old images and associations are recalled through creative and recreative productions. N. Y.

Pathology of Tropical Diseases. By Col. J. E. Ash and Sophie Spitz, M.D. Pp. 350; 941 ills. Phila., Saunders, 1946. Price, $8.00.

The morbid changes which characterize many of the so-called Tropical Diseases usually are described briefly and often incompletely in textbooks of Tropical Medicine. Likewise textbooks of pathology usually give little attention to these diseases, if they do not omit consideration of them altogether. Thus this volume fills a great need. The following list of infections and other diseases will serve to indicate the contents of the books: (1) Virus diseases; (2) Rickettsial diseases; (3) Spirochetal diseases; (4) Dysenteries; (5) Bacterial diseases; (6) Fungus infection; (7) Diseases caused by Protozoa of the blood and tissues; (8) Nematodes; (9) Trematodes; (10) Cestodes; (11) Diseases caused by environmental factors; and (12) Deficiency diseases. Each of the diseases is defined briefly, with short sections on epidemiology, clinical features and pathology. A short list of references is given at the end of each section, followed by the plates illustrating the characteristic morbid changes. These include photographs of patients and of gross and microscopic specimens, each well chosen. It is difficult in so short a review to do justice to the excellence of the book. One may find an occasional error in a legend or wish for a somewhat more modern viewpoint in the presentation of pathologic physiology; but these faults shrink into insignificance when the whole is considered. It is difficult to see how the selection of material might have been bet-

tered. The authors have drawn the best from a great wealth of information and presented it in a highly skilful manner. They and their publisher deserve more than congratulations. H. R.

GROUP PSYCHOTHERAPY: THEORY AND PRACTICE. By J. W. KLAPMAN, M.D., Faculty, Northwestern University Medical School. Pp. 332. New York: Grune & Stratton, 1946.

GROUP psychotherapy has enlisted new interest during recent years. Though, as the author points out, it is not entirely new, this is the first serious attempt to write a book encompassing the field and formalizing the technique. Every worker in group psychotherapy starts with certain assumptions or premises, most of which are discussed briefly, developing certain theories concerning the technique to be used. The text shows that the author has read extensively in the field and his references are well selected. Case examples handled by different group psychotherapy techniques are cited and are explained as demonstrations of favorable or unfavorable reactions. These various techniques include the psychodrama, reëducation, and group psychotherapy in private psychiatric practice, in the mental hospital, and with problem children. Methods to be used in the organization of groups are also mentioned. The book is easy to read and has a reasonable viewpoint about the uses of Psychotherapy. It should be read by every professional and lay person interested in the "Group," as it is a definite step ahead in the development of literature on the subject. L. S.

AGNOSIA, APRASIA, APHASIA. Their Value in Cerebral Localization. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Assistant Clinical Professor of Medicine (Neurology), University of Southern California. 2nd ed. Pp. 286; 59 ills. New York: Hoeber, 1946. Price, $5.00.

THE first edition of Dr. Nielsen's work, published 10 years ago, aroused considerable interest and also controversy; largely because the conclusions that were tentatively advanced were at decided variance with the accepted, albeit admittedly muddled, concepts of aphasias. Since that time, Dr. Nielsen has continued an exhaustive study of this field and has had access to a large amount of clinical material. In the present edition, he further elucidates the results of his work on speech disorders and cerebral localization. Of particular interest is the material on the rôle played by the minor hemisphere and interhemispheric shifting of language functions. These important concepts, while not new, have received little attention in previous works on this subject.

The author presents his material in 3 sections: Part 1 contains an historical introduction and a general discussion of agnosia, aphasia and apraxia. Part 2 includes a chapter on methods of examination which will be of help to the clinician. The author points out the pitfalls in the usual methods of testing for the aphasias and describes a variety of tests useful in eliciting the different defects. The bulk of this section is devoted to clinico-pathologic abstracts of 136 important case histories, verified by surgery or autopsy, which illustrate the conclusions reached on the location and interrelationship of language centers. Many of these are cases which were studied personally by the author. He has also drawn heavily on Henschen's detailed monograph. Part 3, which is entitled Appendix, might preferably be read first. It contains brief, clear discussions of the cerebral areas involved and their significance in language and mentation. A complete list of the terms used, with their definitions, is also included in this section.

Dr. Nielsen's proposed nomenclature does not introduce any marked changes, but does do much to clarify and standardize the terminology now in use—something that is badly needed.

This book is recommended to neurologists, psychologists and anyone interested in problems of cerebral localization. W. H.

EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION. By LOUIS N. KATZ, A.B., M.A., M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Professorial Lecturer in Physiology, University of Chicago. 2nd ed. Pp. 288; 141 ills. Phila.: Lea & Febiger, 1946. Price, $6.00.

ACCORDING to the author's Preface, "The revision of this book was undertaken in order to continue to meet this need in terms

of the new electrocardiographic knowledge and terminology incorporated in the revision of the companion book on electrocardiography." This edition preserves the format of the first, with description, interpretation and clinical correlation adjacent to the full page reproduction of the electrocardiogram in each instance. W. J.

CLINICAL LABORATORY DIAGNOSIS. By SAMUEL A. LEVINSON, M.S., M.D., PH.D., Director of Laboratories, Research and Educational Hospital, Chicago; Professor of Pathology, University of Illinois College of Medicine; and ROBERT F. MACFATE, CH.E., M.S., PH.D., Assistant Director of Laboratories, Research and Educational Hospitals; Assistant Professor of Pathology, University of Illinois College of Medicine. 3rd ed. Pp. 971; 192 engravings and 15 plates. Phila.: Lea & Febiger, 1946. Price, $10.00.

THIS manual covers a rather wider range of subject matter than do most of such manuals and describes at least 1 procedure for each purpose in great detail, step by step. The Reviewer has had no opportunity to test the freedom from typographic errors in these detailed quantitative descriptions, formulas, graphs and tables; but the success of 2 previous editions invites confidence.

Procedures applicable in the field of legal medicine and toxicology, procedures and values appropriate in pediatric practice, a chapter on laboratory study of so-called tropical diseases, a chapter on skin tests, and 1 on milk and water analysis are included. Especially if the specialized monographs in different fields are not available, will this manual be a useful guide and source of information.

There are many well-chosen illustrations. The field covered, however, is so wide that even this generous allowance cannot, of course, compete with the illustrative material available in a library of special monographs covering various fields. Theoretical considerations are severely condensed and are presented in a number of instances in schematic form. The amount of technique and information condensed here in a single volume is noteworthy. J. A.

NEW BOOKS

Merrilleana. A Selection From the General Writings of ELMER DREW MERRILL, SC.D., LL.D., Arnold Professor of Botany, Harvard University; former Director, Bureau of Science, Manila; Dean, College of Agriculture, University of California; Director, New York Botanical Garden; Administrator of Botanical Collections, Harvard University, and Director, Arnold Arboretum. Chronica Botanica, Vol. 10, No. 3/4. Pp. 393; 24 ills. Waltham, Mass.: The Chronica Botanica Co., 1946. Price, $4.00.

THOUGH only indirectly connected with Medical Science, this volume contains interesting matter of general biologic interest, written by "the American Linnaeus."

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

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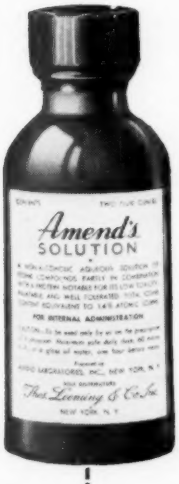

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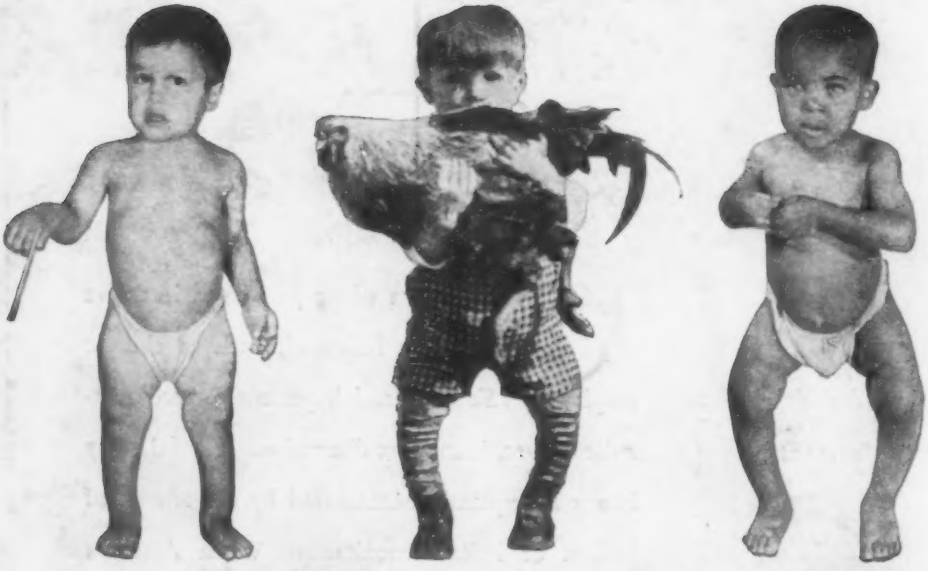

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